EXHIBIT 41

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO:*** ***Newsome, et al. v. Johnson & Johnson, et al.*** ***3:18-cv-17146***	**MDL NO. 16-2738 (MAS) (RLS)**

SECOND AMENDED RULE 26 EXPERT REPORT OF DANIEL L. CLARKE-PEARSON, MD

Date: May 28, 2024

Dan Clarke-Pearson MD

Daniel L. Clarke-Pearson, MD

I am a Professor in the Department of Obstetrics and Gynecology and the Division of Gynecologic Oncology at the University of North Carolina. I am certified by the American Board of Obstetrics and Gynecology as a specialist in obstetrics and gynecology as well as a subspecialist in gynecologic oncology.

SUMMARY OF OPINIONS

I was asked to provide my opinion in response to the following questions:

(a) Can the use of talcum powder in the genital area cause epithelial ovarian cancer (EOC)? and

(b) If so, what is the biological mechanism for this occurrence?

It is my opinion, to a reasonable degree of medical and scientific certainty, that the use of talcum powder products, including Johnson's Baby Powder and Shower to Shower, applied to the perineum of women, can cause EOC. My opinion is based on research that I have conducted in the medical and scientific literature as well as my knowledge and experience as an obstetrician-gynecologist and as a subspecialist in gynecologic oncology for over 40 years.

The increased risk associated with the genital use of talcum powder has been consistently described over decades in numerous studies. The mechanism by which talcum powder causes cancer involves: 1) ascension of particles to the fallopian tubes and ovaries; and 2) initiation of a chronic inflammatory process that includes oxidative stress and specific genetic mutations.

My opinion that genital application of talcum powder is a significant risk factor for all users and can cause epithelial ovarian cancer in some women by an accepted mechanism is strongly supported by credible scientific research. When formulating my opinions regarding causality, I considered the extensive body of literature in its totality, weighing the data and information according to its importance using the concepts outlined by Bradford Hill. The Bradford Hill factors include strength of association, consistency, specificity, temporality, biologic gradient, biologic plausibility, coherence, experiment, and analogy. These are discussed in detail later in this report.

QUALIFICATIONS

The focus of my clinical practice, teaching and research for the past 40 years has been the care of women with gynecologic cancers (cancers of the ovary, fallopian tube, uterus, cervix, vagina, and vulva). In addition, I also provide care for complex gynecologic surgical problems (endometriosis, large ovarian tumors, leiomyomata).

I received a BA from Harvard College (major in biology). I spent a year as a laboratory technician developing a device to noninvasively detect deep venous thrombosis. I then attended medical school at Case Western Reserve University School of Medicine (Cleveland, OH). After graduating in 1975, I completed a four-year residency in Obstetrics and Gynecology at Duke University Medical Center (Durham, NC). I then completed a three-year fellowship in Gynecologic Oncology at Duke. From 1982-1985, I was an assistant professor on the Duke faculty (Division of Gynecologic Oncology). From 1985-1987, I was the Director of Gynecology and Gynecologic

Oncology at the University of Illinois (Chicago, IL). I returned to Duke in 1987 to serve as the Director of Gynecologic Oncology and Director of the Gynecologic Oncology Fellowship program. I was appointed a full professor with tenure and was awarded a Distinguished Professorship (James Ingram Professor of Gynecologic Oncology) in 1993.

From 2005 until 2019, I served as Chair of the Department of Obstetrics and Gynecology at the University of North Carolina (Chapel Hill, NC). As the Robert A. Ross Distinguished Professor and Chair, I had administrative responsibilities for over 75 faculty, 28 residents in obstetrics and gynecology and 29 fellows receiving subspecialty training in eight subspecialties. Throughout my career, I provided clinical care to women with gynecologic cancers including surgery, administration of chemotherapy, and conducting clinical trials. Currently, I have a part-time position in the department and continue to educate medical students and residents in Obstetrics and Gynecology and Fellows in Gynecologic Oncology.

I have published over 250 peer-reviewed manuscripts in the medical literature. I have also written over 50 chapters for medical textbooks and edited three medical textbooks. My research has focused on the treatment of gynecologic cancers, surgical techniques, and the prevention of venous thromboembolic (VTE) disease. I have conducted the practice defining clinical trials evaluating various methods to prevent VTE in gynecologic surgery.

I have served on the editorial boards of four peer-review journals (*Obstetrics and Gynecology, Journal of Gynecologic Techniques, Journal of Gynecologic Surgery* and *Gynecologic Oncology*). I served as a board examiner for the American Board of Obstetrics and Gynecology for eighteen years. I have been actively involved with relevant medical organizations including the American College of Obstetricians and Gynecologists (ACOG), the Society of Gynecologic Oncology (SGO), the American College of Surgeons (ACS) and the Gynecologic Oncology Group (GOG). I have led numerous postgraduate continuing education courses sponsored by ACOG. Most have focused on teaching obstetricians and gynecologists complex pelvic surgery and management (and prevention) of surgical complications. I have served on several ACOG committees (Technical Bulletins, Gynecologic Management and Grievance) and was the chair of the Gynecologic Management Committee that wrote Clinical Opinions distributed to ACOG members. I also served a three-year term on the ACOG Executive Board. As a gynecologic oncologist, I have been an active member of the SGO and have served on a number of SGO Committees and the Executive Board. In 2010, I was the SGO President. As a member of the American College of Surgeons, I have presented CME lectures at the ACS annual meeting and have served on the ACS Obstetrics and Gynecology Advisory Committee and the Commission on Cancer. The GOG is a cooperative group organization sponsored by the National Cancer Institute to conduct clinical trials investigating new treatments to improve the outcomes of women with gynecologic cancers. Many of the publications on my CV (Exhibit A) derive from participation in these clinical trials.

I am a past member of the SGO Ethics Committee, past President of the Council of University Chairs of Ob Gyn (CUCOG), and currently serve as the President-Elect of the Society of Pelvic Surgeons.

My updated *curriculum vitae* is attached as **Exhibit A.**

METHODOLOGY AND MATERIALS REVIEWED

Specifically, in preparing this report, I sought to obtain relevant information through several sources. I primarily relied on a PubMed search of "talc AND Ovarian Cancer", "Ovarian Cancer AND risk factors", "Talcum Powder AND Ovarian Cancer", "Talcum Powder AND Cancer", "Talc AND Cancer", "Asbestos AND Ovarian Cancer", "Asbestos AND Cancer". These searches provided peer-reviewed papers that included original research, case-controlled studies, cohort studies, meta-analysis studies, and review papers and systematic analysis. I also searched some of the references cited in these papers. Google searches were also performed. I also reviewed a number of textbooks searching for "ovarian cancer risk factors" and "talc/talcum powder". In addition to the literature derived from these searches, I received relevant materials at my request to clarify a particular topic or answer a question. I approached this research with the same scientific rigor that I would use in my own clinical, academic, and research practice.

I assessed the data and conclusions of these peer-reviewed articles considering the strengths and weaknesses of each particular study. The medical and scientific literature on these topics varies in the quality of the study design and, at times, in conclusions. I approached each article objectively and critically, assessing for factors such as design, power, reputation of author(s), quality of journal, and potential biases. The increased risk associated with the genital use of talcum powder is consistently described over decades.

When formulating my opinions regarding causality, I considered the extensive body of literature in its totality, weighing the data and information according to its importance using the concepts outlined by Bradford Hill. Overall, I believe that the opinions expressed in this report are strongly supported by credible scientific research. The complete list of the materials I considered is attached as **Exhibit B**.

BACKGROUND AND OPINIONS

a) Overview of Ovarian Cancer

Approximately 20,000 women in the US will be diagnosed with ovarian cancer annually. To date, there is no method to screen for ovarian cancer and symptoms associated with ovarian cancer are vague and not specific. Therefore, at the time of initial diagnosis, nearly 75% of women will have ovarian cancer spread throughout the abdominal cavity, lymph nodes and into the lung (pleural effusion). Current treatment includes initial surgery to attempt to remove the bulk of the cancer ("debulking surgery") followed by treatment with multi-agent chemotherapy. Unfortunately, the majority of women will ultimately die from this malignancy.

Ovarian cancer refers to a group of malignancies found in the ovary. These groups are determined based on the ovarian cells from which they arise – germ cell, stromal, and epithelial cancers. Epithelial ovarian cancers (EOC) involve the cells on the surface of the ovary and can originate in either the ovary or fallopian tube. These account for the vast majority of ovarian cancers (greater than 90%). EOC are further subdivided based on the microscopic characteristics of the cells. These subtypes include serous, endometrioid, clear cell, mucinous, undifferentiated, or mixed. Of these, serous is by far the most common at approximately 70% of EOCs.

b) Pathogenesis of Ovarian Cancer

There are several theories as to the origin of ovarian cancer. One holds that "incessant ovulation" requires "repair" of the ovarian surface epithelium after each ovulation. The "repair" mechanism is prone to generate DNA errors (mutations) that result in malignant transformation. (Fathalla 1971). This theory is supported by observations that events that reduce ovulation are associated with a lower risk of a woman developing ovarian cancer. Pregnancy, breast feeding, and use of oral contraceptives all reduce the risk of ovarian cancer. (Havrilesky et al. 2013; La Vecchia 2017).

Before 2008, it was presumed two other cancers in women (fallopian tube and primary peritoneal) were distinct from ovarian cancer. However, Levanon recognized that many EOCs actually arise in the fallopian tube and metastasize to the ovary and peritoneal cavity. (Levanon, Crum, and Drapkin 2008). This observation is supported by molecular data (especially the frequent finding of P53 mutations in the fallopian tube and EOC metastases). (Fathalla et al. 2013; Kurman and Shih 2016; Dubeau and Drapkin 2013; Chien et al. 2015). Today, we believe that EOC, fallopian tube carcinoma and primary peritoneal carcinoma are the same entity and share similar risk factors and pathogenesis.

By definition, cancer results from gene mutations in normal cells that transform the normal cell into a cell that has lost its regulation of controlled growth. Mutations can occur through a number of processes. Some mutations may be inherited from either the patient's mother or father. BRCA1, BRCA2 and mismatch repair gene (Lynch Syndrome) mutations are such examples. In most instances, the mutations occur due to exposures such as virus (HPV virus causing cervical, anal, vulvar and oropharyngeal cancers), tobacco smoking (lung cancer) and exposure to x-rays (leukemia). Some exposures result in a chronic inflammatory response that induces mutations as the normal cell attempts to repair damage such as that caused by asbestos (pulmonary mesothelioma, ovarian cancer). These mutations can also occur spontaneously as cells (and individuals) age. (Bottazzi, Riboli, and Mantovani 2018).

c) Inflammation and Cancer

There is a clear link between inflammation (resulting in oxidative stress) and cancer risk. This is true for many types of cancers, including stomach, colon, cervix, mesothelioma, pancreas, and liver, as well as ovary. (Balkwill and Mantovani 2001; Coussens and Werb 2002; Okada 2007; Reuter et al. 2010; Crusz and Balkwill 2015; Fernandes 2015). Inflammation causes cancer through promoting cell proliferation, oxidative stress, DNA damage and gene mutations. This process is associated with many steps in the genesis of cancers including initiation, progression, metastases and chemoresistance.

Both inflammatory cells and cancers produce cytokines and chemokines that contribute to cancer growth and spread. Cytokines, particularly TNF-alpha and IL-1 beta, generate reactive oxygen species (ROS) and reactive nitrogen species (RNS). These are potent mutagens and are comparable to the cell damage caused by ionizing radiation. (Yan et al. 2006). These ROS radicals cause DNA breaks and DNA adducts. The inflammation cascade has been shown to occur in the pathogenesis of EOC. (Shan and Liu 2009; Saed, Diamond, and Fletcher 2017; Khan et al. 2011; Saed et al. 2018; Trabert et al. 2014; Savant et al. 2018; Ding et al. (2021)). Fletcher and Saed exposed normal

ovarian cells and EOC cells to talcum powder and demonstrated significant cellular effects including oxidative stress, cell proliferation, decreased apoptosis, and enzymatic activity corresponding to single nucleotide polymorphisms (SNPs) associated with inflammation and ovarian cancer. (Harper et al. 2019). Recently, Harper and Saed also demonstrated that exposure to Johnson's Baby Powder causes p53 mutations, cell proliferation and malignant transformation in normal ovarian epithelial cells. (Harper et al. 2023).

Talcum powder is known to elicit an inflammatory response in animals and humans. (Eberl and George 1948; Radic et al. 1988; NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) (NonAsbestiform) in F344/N.Rats and B6C3Fl Mice (Inhalation Studies) 1993). Shukla demonstrated *in vitro* that crocidolite asbestos and non-fibrous (platy) talc caused expression of genes in ovarian epithelial cells producing inflammatory cytokines. (Shukla et al. 2009). Gates documented absence of some DNA repair mechanisms in patients who were genital talcum powder exposed when compared to controls in the New England Case Control Study. (Gates et al. 2008). In another series of *in vitro* experiments, Buz'Zard transformed normal ovarian epithelial cells to malignant cells by talc exposure. (Buz'Zard and Lau 2007). Akhtar et al. (2010, 2012) also demonstrated oxidative stress in cells exposed to talc particles. Yan and Kahn have demonstrated similar findings in their laboratories. (Yan et al. 2006; Khan et al. 2011). In 2020, Mandarino demonstrated that talc, especially in combination with estradiol, stimulated macrophages to produce increased reactive oxygen species and changes in gene expression that could promote a pro-tumorigenetic environment. (Mandarino et al. 2020). In 2021, Emi et al. conducted a follow-up study which found that the "pathway affected by talc included cell proliferation, immune responses, and signaling, immunosurveillance, apoptosis." (Emi et al. 2021). These studies provide evidence of chronic inflammation in animals and cells when exposed to talcum powder and support the findings of experiments with Johnson's Baby Powder. (Fletcher et al. 2019).

d) EOC Risk Factors

Inherited mutations such as BRCA1 and BRCA 2 are the most significant risk factors for epithelial ovarian cancer. The lifetime risk of developing ovarian cancer is 39-46% in BRCA1 carriers and 11-27% in women with BRCA 2 mutation. (Ring et al. 2017). This is compared to 1.3% lifetime risk in non-carriers. Mutations in BRCA1 and BRCA2 make up 75% of all hereditary ovarian cancers, but only account for 10-15% of all EOC. (Lancaster 2015).

Women with hereditary risk are also affected by genetic modifiers, including nongenetic and environmental factors. (Levy-Lahad 2007). Environmental factors would include exposure to talcum powder and asbestos.

Additional risk factors, both nonmodifiable and modifiable, include increasing age, family history of ovarian or breast cancer, nulliparity, early menarche or late menopause, high fat diet, infertility, endometriosis, polycystic ovarian syndrome, hormone replacement therapy, IUD use, history of pelvic inflammatory disease, obesity, and genital use of talcum powder. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018; IOM 2016; Lheureux 2019; Phung et al. 2022). Ovarian cancer is often multifactorial; risk factors can be cumulative and synergistic. (Vitonis 2011; Wu 2018).

Multiparity, breast feeding, oral contraceptive use, tubal ligation, salpingoophorectomy, and hysterectomy (without salpingoophorectomy) reduce the risk of developing EOC. (Hunn and Rodriguez 2012; Mallen, Townsend, and Tworoger 2018; Park et al. 2018; Folkins et al. 2018).

e) Talcum Powder, Asbestos and other carcinogens

During my postgraduate (residency) training (1975-1979) in obstetrics and gynecology it was reported that talc had been identified deeply imbedded in ovarian cancer tissue samples (Henderson 1971) and raised questions about the association between talcum powder and asbestos. In subsequent studies, Henderson confirmed that these findings did not represent surface contamination. (Henderson et al. 1974; Henderson et al. 1979). It seemed plausible that asbestos (a known carcinogen) could be an EOC risk factor. However, we were taught that asbestos had been removed from talcum powder in the production process.

As a young gynecologic oncologist, it was reassuring to learn that asbestos was no longer contained in talcum powder because we knew that asbestos was a potent carcinogen. IARC monograph 100c (2012) clearly summarizes the evidence associating asbestos to mesothelioma and cancer of the lung, larynx, and ovary. Experimental models demonstrate sufficient evidence for the carcinogenicity of all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthophyllite) and that all forms, as well as talc containing asbestiform fibers, are carcinogenic to humans. Specifically addressing the increased risk of EOC in women exposed to asbestos in occupational settings, there are at least five cohort mortality studies (Acheson et al. 1982; Wignall and Fox 1982; Germani et al. 1999; Berry, Newhouse, and Wagner 2000; Magnani et al. 2008), two population-based cohort studies (Vasama-Neuvonen et al. 1999; Pukkala et al. 2009) and a case control study (Langseth and Kjaerheim 2004) showing a causal association between exposure to asbestos and ovarian cancer.

In the late 1970s concerns that talc could be associated with EOC were expressed by Woodruff and Longo. (Woodruff 1979). The hypothesis suggested that talc applied to the perineum (vulva) ascends to the vagina and then into the uterus and through the fallopian tubes to implant on the ovary and other peritoneal surfaces. This foreign body was known to create a potent inflammatory reaction when found in the lungs, pleural cavity and peritoneal cavity. In fact, as gynecologic surgeons, we were taught to wash the talcum powder off of our surgical gloves before opening the abdomen to prevent inflammatory reactions and adhesions.

In 1982, a case-control study was the first epidemiologic study alerting the medical community of the possible association of talc use and EOC. (Cramer et al. 1982). Cramer compared women who did and did not use talc in their perineal hygiene. Regular use of talc was found to be associated with an increased occurrence of EOC by 92% (OR of 1.92., 95% confidence interval: 1.27-2.89). Cramer wrote, “It is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates.”

Talcum powder also contains other carcinogens including asbestos, talc containing asbestiform fibers (fibrous talc), heavy metals such as nickel, chromium and cobalt (possible 2b), and other

inflammatory agents, toxins, and carcinogens contained in the fragrance chemicals in talcum powder. (Expert Report of Longo and Rigler 2019; Exhibit 28, Deposition of John Hopkins, Ph.D., MDL No. 2378, 2018; Exhibit 47, Deposition of Julie Pier, MDL No. 2738, 2018; Expert Report of Michael Crowley, Ph.D., MDL No. 2738, 2018). In the analysis of historical samples of J&J talcum powder products performed by Drs. Longo and Rigler, asbestos was present in the majority of samples with fibrous talc (talc fibers) seen in virtually all bottles tested. (Longo and Rigler report). In October 2019, FDA found asbestos in a sample of Johnson's Baby Powder purchased online, resulting in Johnson & Johnson recalling one lot of the product – 33,000 bottles. (BMJ 2019).

Fibrous talc (synonymous with talc in an asbestiform habit, asbestiform talc, or talc fibers) and all forms of asbestos are recognized by IARC as carcinogenic to humans, including ovarian cancer. (IARC 2012). According to IARC, consumer products are the primary sources of talc for the general population (non-occupational). Inhalation and perineal application and migration of talcum powders are the primary routes of exposure. (IARC 2012). The carcinogenicity of asbestos and other mineral fibers involves inflammation, oxidative stress, DNA damage and mutation, inducement of cell proliferation and transformation, and resistance to apoptosis. (IARC 2012, Moller 2013, Mossman 2018, Egilman 2019).

f) Epidemiology Studies

The association of talcum powder and EOC is based on several types of epidemiologic studies. Of course, a randomized controlled double-blinded trial would be more conclusive. However, a randomized trial would be unethical given the evidence that talcum powder causes EOC.

When looking at these epidemiologic studies in their totality, the data shows a consistent, statistically significant increased risk of developing EOC with perineal talcum powder use. Overall, the risk is increased 20-60% when compared with women who did not use talcum powder.

The original case control study published by Cramer et al. in 1982 evaluated the use of perineal talcum powder in 215 white women with EOC (29 cases were "borderline" or ovarian cancer of low malignant potential). These women with EOC were matched by race, age and residence to 215 women in the same community. Talc exposure from surgical gloves, diaphragm use, and perineal use was ascertained. Talc was used by 42.8% of women with EOC and only 28.4% of women who did not have EOC. Any perineal talc exposure showed a statistically significant relative risk of 1.92 (95% confidence limits 1.27-2.89), equivalent to a 92% increased chance of developing EOC. (Cramer et al. 1982).

Subsequently, there have been at least 24 other case-control studies looking at the association of talc and EOC. Overall, the case-control studies show a 30-40% increased risk of EOC associated with genital talcum powder use. These individual studies vary in size and quality, and I weighted them accordingly. Three recent case-control studies replicated previous studies showing an increased risk of EOC in women using perineal talcum powder. Wu evaluated 1701 Californian women with EOC and found talc significantly increased the risk of EOC by 40% in whites, 20% in Hispanics and 56% in African Americans. (Wu et al. 2015). Owing to the small number of

African American women in this study, the findings were not statistically significant.

Subsequently, the National Cancer Institute sponsored a multi-center study of African American women and found a 44% increase in EOC associated with talc use. A dose-response was also found for duration of use and number of lifetime applications ($p<.05$). (Schildkraut et al. 2016). Cramer performed a case control study (with additional pooled data) in 2016 that included nearly 4,000 women with EOC finding an elevated EOC risk of 33% (OR 1.33, 95% CI 1.16, 1.52). Risk increased with frequency and duration of use. (Cramer et al. 2016).

I also reviewed four cohort studies (Gertig, Gates, Houghton, Gonzalez). While not addressing talcum powder usage as the primary research question, these studies also reported the relationship between powder usage and ovarian cancer. The Gertig study showed a statistically significant increased risk of serous epithelial ovarian cancer with talcum powder users. However, I found these studies to have significant limitations due to defective trial design and reporting of their data.

Recently, O'Brien et al. published a pooled study of the data from four cohort studies. The authors concluded that there was not a statistically significant association between the genital use of powder and an increased risk of ovarian cancer. (O'Brien et al. 2020). However, closer examination of the data indicates a significant increased risk in women with an intact reproductive tract. Additional criticisms of the paper are outlined in Letters to the Editor (from Drs. Cramer, Harlow, Murray, and Rothman) and include the possibility of the study being underpowered, the discordance between the findings and conclusions of the authors, the lack of consistency among the cohort inquiries, and the failure to take into account the age and menopausal status of the subjects. (O'Brien et al. 2020; Gossett 2020; Letters to Editor JAMA 2020).

While case-control studies and cohort studies are compelling, in my opinion, meta-analysis studies are much stronger in that they include larger numbers of patients resulting in greater statistical power. I reviewed eight meta-analyses, one pooled study (Terry) and one cohort-only pooled study (O'Brien) reported between 1995 and 2022. All of these studies, with the exception of O'Brien, report a statistically significant increased risk of EOC in women who use talcum powder in the genital area.

Penninkilampi reported that there was a further increase in EOC in women who used talcum powder more frequently. In those who had greater than 3,600 lifetime applications the odds ratio increased to 1.42 (OR 1.42; 95% CI 1.25-1.61) when compared with women who used < 3,600 applications (OR 1.32; 95% CI 1.15-1.50). In this study, talcum powder use was associated with an increased incidence of endometrioid and serous EOC but not mucinous or clear cell types. (Penninkilampi and Eslick 2018). These results were similar to the meta-analysis conducted by Berge et al. (2018), summary relative risk 1.22 (95% CI: 1.13–1.30).

The Taher meta-analysis was commissioned by Health Canada and formed the epidemiological basis for its assessment of the risks of cosmetic talc (non-asbestos containing). Health Canada performed an extensive review of the subject that included a Bradford-Hill analysis and concluded: "With regards to perineal exposure, **analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer**. The available data are indicative of a

causal effect. Given that there is potential for perineal exposure to talc from the use of certain self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath), a potential concern for human health has been identified." (Health Canada Assessment 2021).

In a recent meta-analysis by Davis, et al. (2021), data from five studies in the Ovarian Cancer in Women of African Ancestry Consortium were considered. Participants included 620 African-American ovarian cancer cases and 2,800 white cases, and 1,146 African-American controls and 6,735 white controls who answered questions on genital powder use prior to 2014. For all cases with frequency of use > once per week, there was an increased risk of 1.31 (95% CI 1.15-1.48), with an odds ratio of 1.31 (95% CI 1.13-1.52) for high-grade serous and 1.29 (95% CI 1.09-1.54) for all other histotypes. The authors concluded that "the associations between genital powder use and ovarian cancer risk were similar across race and did not materially vary by histotype."

In a study performed by the Ovarian Cancer Association Consortium, the data of 9 case-controlled studies were pooled to consider the effect of well-established ovarian cancer risk factors in women with endometriosis and without endometriosis. The pooled analysis included 8500 women with ovarian cancer and 13,592 controls. For women with endometriosis, an inflammatory process, the increased risk of ovarian cancer with genital talc use was 38% (OR 1.38, 95% CI 1.04-1.84); for women without endometriosis, the increased risk was 12% (OR 1.12, 95% CI 1.01-1.25). (Phung et al. 2022).

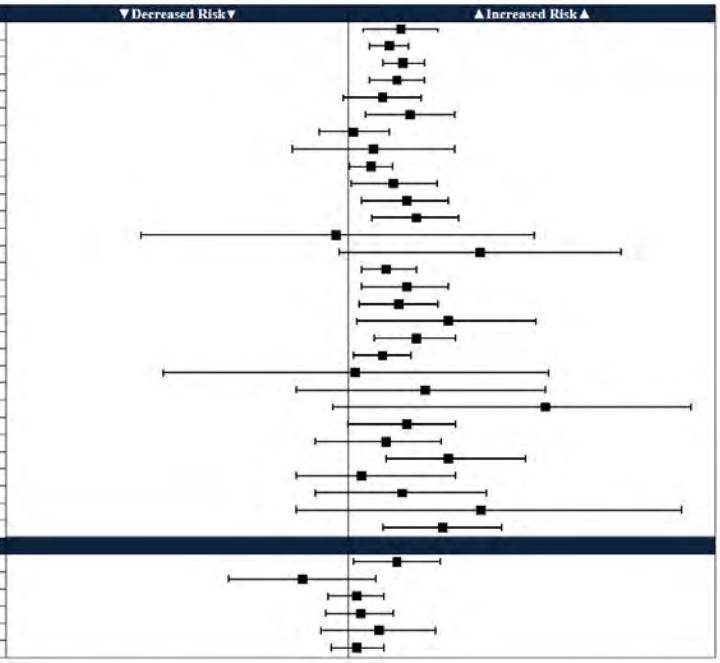
Woolen, et al. (2022) conducted a systematic review and meta-analysis of eleven studies, focusing on frequent use of genital talc which was defined as ≥ 2 times per week. "Frequent talcum powder use was associated with an elevated risk of ovarian cancer (adjusted pooled summary odds ratio 1.47 (95% CI 1.31, 1.65, P<0.0001)."

With new data from the Sister Study, O'Brien, et al. (2024) published a study showing "in models adjusted for exposure misclassification, genital talc use was positively associated with ovarian cancer (HR range, 1.17-3.34)." Women who used talc frequently had an increased risk of 1.81 (1.29 to 2.53), and women who used genital talc long-term (≥2 decades) had an increased risk of 2.01 (1.39 to 2.91). Genital use of talcum powder by women during their 20s resulted in an increased risk of 1.88 (1.37 to 2.57) and for those women who used in their 30s, 2.08 (1.50 to 2.89). For these data points, the study found an increased risk of ovarian cancer with and without correction for recall bias.

In summary, when evaluating all epidemiological studies, there is a consistent and statistically significant increased risk of developing EOC with perineal talcum powder use. Data from the case control, cohort, meta-analysis, and pooled studies are shown in the following forest plots prepared at the direction of Dr. Anne McTiernan:

Figure 2: Case-Control and Cohort Studies

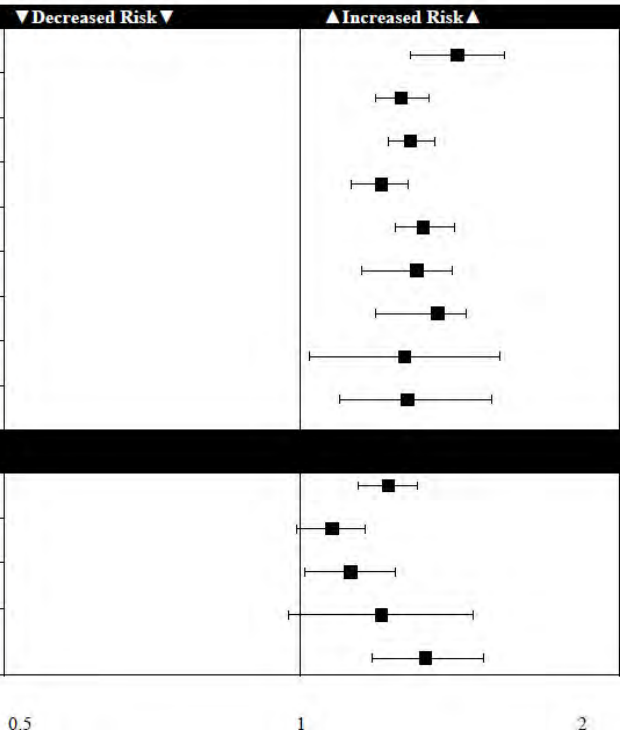
Case-Control Studies	Natl	Cases	Controls	Pop	DR	RR	CI L	CI U
Schildkraut (2016)	US	584	745	Pop.	Yes	1.44	1.11	1.86
Cramer (2016)	US	2041	2100	Pop.	Yes	1.33	1.16	1.52
Wu (2015)	US	1791	2391	Pop.	Yes	1.46	1.27	1.69
Kurta (2012)	US	902	1802	Pop.	N/A	1.4	1.16	1.69
Rosenblatt (2011)	US	812	1313	Pop.	No	1.27	0.97	1.66
Wu (2009)	US	609	688	Pop.	Yes	1.53	1.13	2.09
Moorman (2009) - Wh	US	1114	1086	Pop.	N/A	1.04	0.82	1.33
Moorman (2009) - AA	US	1114	1086	Pop.	N/A	1.19	0.68	2.09
Merritt (2008)	Aus	1576	1509	Pop.	Yes	1.17	1.01	1.36
Mills (2004)	US	256	1122	Pop.	No	1.37	1.02	1.85
Ness (2000)	US	767	1367	Pop.	Inspl	1.5	1.1	2.0
Cramer (1999)	US	563	523	Pop.	Yes	1.6	1.18	2.15
Wong (1999)	US	499	755	Hosp.	Inspl	0.92	0.24	3.62
Godard (1998)	Can	170	170	Pop.	N/A	2.49	0.94	6.58
Green (1997)	Aus	824	855	Pop.	Inspl	1.3	1.1	1.6
Cook (1997)	US	313	422	Pop.	No	1.5	1.1	2.0[1]
Chang (1997)	Can	450	564	Pop.	No	1.42	1.08	1.86
Shushan (1996)	Isr	200	408	Pop.	N/A	2	1.06[2]	3.66[2]
Cramer (1995)	US	450	454	Pop.	N/A	1.6	1.2	2.1
Purdie (1995)	Aus	824	860	Pop.	N/A	1.27	1.04	1.54
Tzonou (1993)	Gre	189	200	Hosp.	N/A	1.05	0.28	3.98
Rosenblatt (1992)	US	77	46	Hosp.	Yes	1.7	0.7	3.9
Chen (1992)	Chn	112	224	Pop.	N/A	3.9	0.9	10.63
Harlow (1992)	US	235	239	Pop.	Yes	1.5	1.0	2.1
Booth (1989) – daily	UK	235	451	Hosp.	Yes	1.3	0.8	1.9[1]
Booth (1989) – wkly	UK	235	451	Hosp.	Yes	2.0	1.3	3.4
Harlow (1989)	US	116	158	Pop.	N/A	1.1	0.7	2.1
Whittemore (1988)	US	188	539	H&P	Yes	1.45	0.81[1]	2.60[1]
Hartge (1983)	US	135	171	Hosp.	N/A	2.5	0.7	10.0
Cramer (1982)	US	215	215	Pop.	N/A	1.92	1.27	2.89
Cohort Studies	**Natl**	**Cases**	**Non**	**Flw Up**	**DR**	**RR**	**CI L**	**CI U**
O'Brien (2024)	US	292	40,536	13	Yes	1.4	1.04	1.89
Gonzalez (2016)	US	154	41,500	6.6	N/A	0.73	0.44	1.2[1]
Houghton (2014)	US	429	61,147	12.4	Inspl	1.06	0.87	1.28
Gertig (2000)	US	307	78,323	N/A	Inspl	1.09	0.86	1.37
Gates (2008)	US	210	600	N/A	Yes	1.24	0.83	1.83
Gates (2010)	US	797	78,323?	N/A	N/A	1.06	0.89	1.28



[1] Corrected data-point from study text (report figure: Cook 1997 CI Upper 2.3; Gonzalez CI Upper 1.21; Booth 1989 CI Upper 1.0; Whittemore CI p=0.06).
[2] Corrected data-point from defense expert report(s) (report figure: p=0.04).

Meta-Analyses and Pooled Studies (All Ovarian)

Meta-Analyses	Studies	Cases	DR	RR	CI L	CI U
Woolen (2022)	11	6542	Yes	1.47	1.31	1.65
Taher (2018)	27	17,149	Yes	1.28	1.2	1.37
Penninkilampi (2018)	27	14,311	Yes	1.31	1.24	1.39
Berge (2018)	27	N/A[1]	Yes	1.22	1.13	1.3
Langseth (2008)	20	N/A[1]	N/A	1.35	1.26	1.46
Huncharek (2003)	16	5260	No[2]	1.33	1.16	1.45
Cramer (1999)	14	3834	N/A	1.4	1.2	1.5
Gross (1995)	10[3]	1509	N/A	1.29	1.02	1.63
Harlow (1992)	6	1106	N/A	1.3	1.1	1.6
Pooled Meta-Analyses	**Studies**	**Cases**	**DR**	**RR**	**CI L**	**CI U**
Terry (2013)	8	8,525	Yes	1.24	1.15	1.33
O'Brien (2020)	4	2168	No	1.08	0.99	1.17
↳ Patent Reproductive Tract	4	1384	Yes	1.13	1.01	1.26
Davis (2021)	5	AA:620 Wh:2800	No	1.22 1.36	0.97 1.19	1.53 1.57



g) Migration and transport of talc particles to the ovaries and other pelvic organs

How is it possible for cosmetic talcum powder, applied to the perineum, to reach the fallopian tube and ovary and cause an inflammatory response that could result in malignant transformation?

As compared to males, the female reproductive tract is open and allows migration of potential pathogens into the peritoneal cavity. The female reproductive tract is in continuity between the peritoneal cavity and the external environment. For example, an ovum extruded from the ovary (an intraperitoneal organ) can progress down the fallopian tube to the uterine cavity, implant and result in a pregnancy that delivers vaginally. The converse is also obvious. It is clearly recognized that sperm (including sperm and sperm particles which would be non-motile) ascend from the vagina through the uterus and into the fallopian tube and into the peritoneal cavity. (Jones and Lopez 2006). Sexually transmitted bacterial infections (for example, gonorrhea and chlamydia) ascend from the vagina to the tube and ovary resulting in pelvic inflammatory disease and tubo-ovarian abscesses. While sperm and bacteria are "motile", non-motile substances have been demonstrated to ascend from the vagina to the peritoneal cavity. As far back as 1961, Egli demonstrated that carbon particles placed in the posterior vaginal fornix were observed in the fallopian tubes within less than one hour in two of three patients tested. (Egli and Newton 1961). Venter and Iturralde placed albumin microspheres labelled with 99mTc into the vagina. (Venter and Iturralde 1979). During pelvic surgery the following day, radioactive levels were found in the tubes and ovaries in nine of 14 cases. Sjösten conducted a trial that showed that powder on gloves used to perform a gynecologic exam resulted in powder detected in the peritoneal fluid, tubes and ovaries one day after the examination. (Sjösten, Ellis, and Edelstam 2004). Likewise, talc has been detected on the ovaries following surgical oophorectomy. (Henderson et al. 1971; Heller, Gordon, et al. 1996; Heller, Westhoff, et al. 1996). In a recent study using correlative light and scanning electron microscopy, morphologically demonstrated talc particles were found in multiple pelvic organ sites, including pelvic tissues and lymph nodes simultaneously. (McDonald 2019). Talc particles and fibers found in pelvic tissues have been shown to be similar to those found in cosmetic talcum powder products, further supporting migration and transport to pelvic organs. (Johnson 2020).

I reviewed the small body of literature suggesting that migration of particles does not occur and do not think these studies are compelling.

I believe that ascension of talcum powder and its constituents through the genital tract is the most important route of exposure. However, inhalation is another plausible mechanism. (IARC 2012; Steiling et al. 2018, Steffen et al. 2020; Health Canada 2021). With either route, at least some of the talcum powder components are likely to be absorbed into the lymphatic system and bloodstream, representing another mechanism for exposure to internal organs.

CAUSATION ANALYSIS

In my opinion, genital application of talcum powder is a significant risk factor for all users and can cause epithelial ovarian cancer in some women by an accepted mechanism. As an academic and practicing physician, I made this determination in the context of Bradford Hill considerations as follow:

Strength and consistency: This opinion is supported by overwhelming epidemiologic evidence showing that the genital use of talcum powder statistically increases a woman's risk of developing EOC by approximately 30 percent (OR 1.31 Penninkilampi 2018; OR 1.28 Taher et al. 2019; OR 1.31 Davis et al. 2021). For frequent users of talcum powder, the risk is higher (e.g., Woolen et al. 2022; O'Brien et al. 2024). All previous meta-analyses reported similar increases in the risk of developing EOC with the use of talcum powder. In my view, especially when considering the severity and frequency of ovarian cancer and the preventable nature of talcum powder usage, this finding is critically important and consistently supported by numerous studies.

Specificity: Based on the epidemiologic studies cited in this report, there appears to be a specific ovarian cancer caused by talcum powder: epithelial ovarian cancer (EOC). Other reproductive cancers do not appear to have an association. This association satisfies this consideration, although I did not weigh this factor to be as important as strength and consistency.

Temporality: In many cancers where there are identified etiologic agents (smoking and lung cancer, HPV infection and cervical cancer) there is a latency period (time from exposure to the onset of the cancer) that can extend over decades. (Nadler and Zurbenko 2014). This concept applies to the latency period of talcum powder use before a woman develops ovarian cancer, thus fulfilling this consideration.

Biologic Gradient/Dose-response: Measuring the "dose" of talcum powder used by an individual woman is difficult to ascertain and has been dependent on recall by the woman. In general, studies have attempted to capture the application "frequency" (daily? Only used on perineal pads during menstrual cycle?) or duration of use (how many years?). In addition, biologic gradient or dose-response is not always linear (e.g., asbestos exposure and mesothelioma is generally thought to have a "threshold response"). A number of studies have demonstrated an association between "dose" and the occurrence of EOC (response). (Terry et al. 2013; Schildkraut et al. 2016; Daniel W. Cramer et al. 2016; Penninkilampi and Eslick 2018; Woolen et al. 2022). More recently, *in vitro* studies have demonstrated a dose dependent effect of talcum powder on molecular changes associated with carcinogenesis. (Fletcher et al. 2019; Mandarino et al. 2020).

Plausibility: This is obviously a critical factor when forming opinions on causation of a risk factor. Evidence shows that talcum powder ascends from the perineum through the vagina, cervix and uterus into the fallopian tubes and onto the ovary. Talcum powder is known to be an agent that causes inflammation. An inflammatory reaction caused by talcum powder on the tube and surface of the ovary results in genetic mutations and carcinogenesis. Talcum powder causes ovarian cancer through this mechanism. The "talcum powder agent" includes numerous constituents such as platy talc, asbestos, fibrous talc, heavy metals and/or chemicals contained in fragrances added to talcum powder, all of which cause an inflammatory reaction leading to carcinogenesis.

Coherence: Epidemiological data, *in vitro* and *in vivo* research are consistent in explaining the pathogenesis of EOC through the inflammatory mechanisms described above. (Saed, Diamond, and Fletcher 2017; Savant et al. 2018; Ding et al. 2021). Further, this is consistent with the causes of other cancers.

Experiment: There are no randomized trials comparing outcomes of women who use or who do not use talcum powder in their perineal hygiene. Further, such a trial at this point in time would be unethical. How could we expose women to talcum powder when the existing evidence supports causation of EOC? Laboratory research (*in vitro*) present evidence to support the biologic, genetic, epigenetic and neoplastic consequence to ovarian epithelium when exposed to talcum powder. (Buz'Zard and Lau 2007; Shukla et al. 2009; Akhtar et al. 2010; Akhtar et al. 2012; Fletcher et al. 2019; Mandarino et al. 2019; Emi et al. 2021; Harper et al. 2023).

Analogy: There are numerous reports in the medical literature of minerals similar to talc causing cancer. Probably the most significant example is asbestos and lung cancer (mesothelioma).

CONCLUSION

It is my opinion, based on research that I have conducted in the medical and scientific literature as well as my knowledge and experience as an obstetrician-gynecologist and as a subspecialist in gynecologic oncology for over 40 years, that the use of talcum powder products including Johnson's Baby Powder and Shower to Shower, applied to the genital area of women, can cause EOC. The mechanism by which talcum powder causes cancer involves: 1) ascension of particles to the fallopian tubes and ovaries and 2) initiation of an inflammatory process that includes oxidative stress and specific genetic mutations. The additional studies that have been published and I have considered since my prior report reaffirm my opinion that the genital use of talcum powder can cause ovarian cancer.

These opinions are made to a reasonable degree of medical and scientific certainty.

I reserve the right to supplement or amend this report if new information becomes available. I reserve the right to review and remark on the reports and testimony of Defendants' experts. My prior testimony is attached as **Exhibit C**.

Tamara Newsome: Brief Medical History
DOB [redacted] 1961

Initial Presentation:

[redacted]

The medical records indicated:

Past Medical History: [redacted].

Past Surgical History: [redacted].

OB/GYN History: [redacted].

Social History: [redacted].

Family History: [redacted]

Allergies: [redacted].

Physical Exam:
[redacted]

Imaging and preoperative evaluation:

[redacted]

[redacted]

Staging Procedure:

[redacted]

Pathology:

[redacted]

Postoperative Treatment Course:

[redacted]

[redacted]

Tamara Newsome: Case-Specific Opinions

I reviewed the available medical records for Ms. Tamara Newsome, Plaintiff Profile Form, deposition testimony, and Dr. Godleski's pathologic findings in considering my opinion regarding causation in this case. My opinions are based on my education, training, and experience, as well as the General Causation facts and opinions contained in this report. After completing my review, it is my opinion that Ms. Newsome's regular use of talcum powder products on her body, including her genital area, is a substantial contributing cause of her ovarian cancer.

Ms. Tamara Newsome has stage IIa endometroid carcinoma of the ovary ([redacted]). She underwent [redacted]

[redacted]

In formulating my opinion regarding causation of Ms. Newsome's ovarian cancer, I considered all the relevant factors that could contribute to the development of her ovarian cancer, forming a differential diagnosis as follows:

1. Is the genital use of talcum powder associated with Ms. Newsome's type of cancer? Yes, she has an epithelial ovarian cancer of the endometrioid subtype. This type of cancer has been associated with genital talcum powder use in multiple studies.

2. Was the duration and frequency of Ms. Newsome's talcum powder usage sufficient to cause ovarian cancer? Yes. Tamara Newsome used Johnson's Baby Powder with talc from 1975-2015 approximately once a day, every day, after showering. [redacted] She estimates using at least 2 large bottles per month. It was part of her daily hygiene routine. Ms. Newsome also used Shower to Shower occasionally when she could not find Johnson's Baby Powder. She estimates buying a total of four bottles of Shower to Shower during her lifetime. She does not recall purchasing Shower to Shower after her son was born in 1993. She applied it in the same way.

   After using talc-based Johnson's Baby Powder exclusively for thirty years, she began using Johnson's Baby Powder with cornstarch interchangeably with the talc-containing variety from 2004 to 2015. In my estimation, this pattern of usage would result in at least 10,000 applications of talc-containing powder over her lifetime.

3. Was there talc and/or asbestos found in her pathologic tissue, providing additional evidence of usage? Dr. Godleski, in his pathologic evaluation, found 30 talc particles, one talc fiber, and one tremolite fiber in Ms. Newsome's tissue. Although not a requirement, these findings provide further evidence to support my causation opinions in this case.

4. Was there enough time between the onset of use and the diagnosis of ovarian cancer to account for the expected latency period associated with the development of ovarian cancer? Yes, she reports use beginning approximately 40 years prior to the diagnosis of her ovarian cancer – consistent with the latency period described with carcinogens causing cancer and talcum powder use causing ovarian cancer.

5. Were other risk factors or protective factors present and, if so, what was their contribution to the development of ovarian cancer?

   Risk Factors:
   - Inherited genetic mutations – [redacted].
   - Family history of ovarian or breast cancer – [redacted].

- Nulliparity – [redacted].
- Early menarche – [redacted].
- Late menopause – [redacted]
- High fat diet – [redacted].
- Infertility – [redacted]
- Endometriosis – [redacted]
- Polycystic ovarian syndrome – [redacted]
- Hormone replacement therapy – [redacted]
- IUD use – [redacted]
- Pelvic Inflammatory Disease – [redacted]
- Obesity – [redacted]

Protective Factors:

- Multiparity – [redacted]
- Breastfeeding – [redacted]
- Oral contraceptive use – [redacted]
- Tubal ligation – [redacted]
- Hysterectomy – [redacted]

In summary, after reviewing the available medical records, Plaintiff Profile Form, deposition testimony, and Dr. Godleski's expert report, it is my opinion that Ms. Newsome's use of Johnson's Baby Powder in the genital area for approximately 40 years is a substantial contributing cause of her ovarian cancer. My opinions are made to a reasonable degree of medical and scientific certainty. I reserve the right to update this report if new information becomes available. I reserve the right to review and remark on the reports and testimony of Defendants' experts.

Exhibit A

Updated: March 2023

UNC SCHOOL OF MEDICINE
CURRICULUM VITAE

Personal Information

Name: Daniel Lyle Clarke-Pearson, M.D.

Address: 105 Porter Place
Chapel Hill, NC 27514

861 Skin Camp Creek
Road
Todd, NC 28684

Phone: (919) 215-9561

Education and Training

Fellow	Duke University Medical Center	1979-1981	Gynecology Oncology
Residency	Duke University Medical Center	1975-1979	Obstetrics and Gynecology
Medical Degree	Case Western Reserve University School of Medicine	1971-1975	Medicine
Bachelor of Arts	Harvard College	1966-1970	Biology

Professional Experience

Professor	University if North Carolina, Chapel Hill	July 2019-present	Obstetrics and Gynecology Division of Gynecologic Oncology
Active Consulting Staff	The Outer Banks Hospital	Oct 2009 – 2012	Medicine/Oncology Section
Chairman	University of North Carolina at Chapel Hill School of Medicine	September 2005 – July 2019	Obstetrics and Gynecology
Robert A. Ross Distinguished Professor	University of North Carolina at Chapel Hill School of Medicine	September 2005 – July 2019	Obstetrics and Gynecology

James M. Ingram Professor of Gynecologic Oncology	Duke University Medical Center	July 1993-2005	Gynecologic Oncology
Division Director	Duke University Medical Center	July 1987-2005	Gynecologic Oncology
Professor	Duke University Medical Center	July 1987-2005	Obstetrics and Gynecology
Director of Gynecology and Gynecologic Oncology	University of Illinois at Chicago	January 1985-1987	Obstetrics and Gynecology
Associate Professor	University of Illinois at Chicago	July1984-1987	Obstetrics and Gynecology
Associate Professor	Duke University Medical Center	January1984	Obstetrics and Gynecology
Co-Director, Trophoblastic Disease Center	Duke University Medical Center	July 1982-1984	Obstetrics and Gynecology
Assistant Professor	Duke University Medical Center	July1980-1984	Obstetrics and Gynecology

Honors and Awards

2022	President-elect, Society of Pelvic Surgeons
2022	Distinguished Service Award, North Carolina Obstetrics and Gynecology Society
2019	UNC Lifetime Achievement Award for Medical Student Education
2009-2010	President, Society of Gynecologic Oncologists
2001-2020	America's Top Doctors for Women (176 Physicians): Women's Health
2008	CREOG National Faculty Award for Excellence in Resident Education
2004	Invited Panel Member, International Consensus Conference of the Prevention of Venous Thromboembolism, Windsor, England
2002	ACOG Roy Pitkin/Elsevier Award: One of top four papers published annually in Obstetrics and Gynecology
2001-present	America's Top Doctors for Women: Women's Health

1991	Invited Panel Participant, Consensus Meeting on the Prevention of Thromboembolism - Windsor, England
1985	Clinical Research Prize Paper – ACOG District Meeting
1981-1984	Junior Faculty Clinical Fellowship – American Cancer Society
1982	Donald F. Richardson Memorial Prize Paper -Best research paper presented by a Junior Fellow at a District ACOG Meeting
1981	Clinical Research Paper, Second Place ACOG Annual Clinical Meeting
1981	Junior Fellow First Prize Paper – ACOG District IV
1980	American Cancer Society Clinical Fellow
1979	Junior Fellow First Prize Paper – ACOG District IV

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Original Research

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213. **Clarke-Pearson DL**, Creasman WT: Diagnosis of deep venous thrombosis in obstetrics and gynecology by impedance phlebography. Obstet Gynecol 58:52, 1981.

214. **Clarke-Pearson DL**, Jelovsek FR: Alterations of occlusive cuff impedance plethysmography results in the obstetric patient. Surg 89:594, 1981.

215. **Clarke-Pearson DL**: Low-dose heparin in prevention of deep venous thrombosis. Am J Obstet Gynecol 138:471, 1980.

216. Wheeler HB, **Pearson DL**, O'Connell D, Mullick SC: Impedance phlebography:Technique, interpretation, and results. Arch Surg 104:164, 1972.

217. Wheeler HB, Mullick SC, Anderson JM, **Pearson DL**: Diagnosis of occult deep vein thrombosis by a noninvasive bedside technique. Surg 70:20, 1971.

Other peer reviewed publications

1. Parker WH, Berek JS, Pritts EA, Olive D, Chalas E, **Clarke-Pearson DL**. Regarding "Incidence of Occult Uterine Malignancy Following Vaginal Hysterectomy with Morcellation". J Minim Invasive Gynecol. 2018; 25: 187-188

2. Parker W, Berek JS, Pritts E, Olive D Kaunitz AM, Chalas E, **Clarke-Pearson D,** et al. An Open Letter to the Food and Drug Administration Regarding the Use of Morcellation Procedures in Women Having Surery for Presumed Uterine Myomas. J Minim Invasive Gynecol. 2016; 23: 303-08.

3. Parker WH, Kaunitz AM, Pritts EA, Olive DL, Chalas E, **Clarke-Pearson DL**, Berek JS. (for the Leiomyoma Morcellation Study Group). U.S. Food and Drug Administration's Guidance Regarding Morcellation of Leiomyoma: Well- Intentioned, but is it Harmful for Women? Obstet Gynecol. 2015.

4. **Clarke-Pearson DL**, Barber EL. Venous thromboembolism in gynecologic surgery: Are we any closer to determining an optimal prophylaxis regimen? (Editorial) Gynecol Oncol. 2015; 138:495- 6

5. Rossi E, **Clarke-Pearson DL**. Screening for Ovarian Cancer in Midlife Women. The Female Patient. 2011; 36: 37-40.

6. **Clarke-Pearson DL**. Clinical practice. Screening for ovarian cancer. N Engl J Med. 2009; 361(2):170-7

7. Alvarez A, **Clarke-Pearson DL**. Platinum-Resistant and Refractory Ovarian Cancer: Second-Line Treatment Options. Am J Cancer 2003; 2: 1-13.

8. Soper JT, Evans AC, Conaway MR, **Clarke-Pearson DL**, Berchuck A, Hammond CB:Evaluation of prognostic factors and staging in gestational trophoblastic tumor. Gest Tropho Tumor 84(6):969-973, 1994.

9. Woolas R, Xu FJ, Jacobs IJ, Yu YH, Daly L, Berchuck A, Soper JT, **Clarke-Pearson DL**, Oram DH, Bast RC Jr: Screeing strategies for ovarian cancer. Diag Oncol 3:287-293, 1993.

10. Nicholaides AN, Areelus J, Belcaro G, Bergqvist D, Borris LC, Buller HR, Caprini JA, Christopoulos D, **Clarke-Pearson D**, et al: Prevention of venous thromboembolism: European consensus statement. Int Angiology II:151-159, 1992.

11. **Clarke-Pearson DL**, Hume RF: Venous thromboembolic disease in Obstetrics and Gynecology: Prevention, diagnosis and treatment. Curr Probl Obstet Gynecol Fertil 12:38-63,1989.

12. **Clarke-Pearson DL**, Olt G: Thromboembolism in patients with gynecologic tumors: Risk factors, natural history and prophylaxis. Oncol 3:39-44, 1989.

13. Beckmann CRB, **Clarke-Pearson DL**, Evenhouse R: A reusable plastic training model for teaching Papanicolaou smear technique. Am J Obstet Gynecol 157:259-260, 1987.

14. Creasman WT, **Clarke-Pearson DL**, Ashe CA, Weed JC Jr: The abnormal pap smear: What to do next. Cancer 48:515, 1981.

ACOG Committee Opinions published during tenure as ACOG Gynecologic Management Committee Chair:

1. Performance enhancing anabolic steroid abuse in women. Committee Opinion No. 484. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;117:1016–18.

2. Understanding and using the U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. Committee Opinion No. 505. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:754–60.

3. Expedited partner therapy in the management of gonorrhea and chlamydia by obstetrician–gynecologists. Committee Opinion No. 506. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:761–6.

4. Management of vulvar intraepithelial neoplasia. Committee Opinion No. 509. American College of Obstetricians and Gynecologists. ObstetGynecol 2011;118:1192–4.

5. Vaginal placement of synthetic mesh for pelvic organ prolapse. Committee Opinion No. 513. American College of Obstetricians and Gynecologists. Obstet Gynecol 2011;118:1459–64.

6. Compounded bioidentical menopausal hormone therapy. Committee Opinion No. 532. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:411–5.

7. Well-woman visit. Committee Opinion No. 534. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:421–4.

8. Reprocessed single-use devices. Committee Opinion No. 537. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012:120:974–6.

9. Risk of venous thromboembolism among users of drospirenone-containing oral contraceptive pills. Committee Opinion No. 540. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012;120:1239–42.

10. Over-the-counter access to oral contraceptives. Committee Opinion No. 544. American College of Obstetricians and Gynecologists. Obstet Gynecol 2012:120;1527-31.

11. Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. Committee Opinion No. 556. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:887–90.

12. Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. Committee Opinion No. 557. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:891–6.

13. Integrating immunizations into practice. Committee Opinion No. 558. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:897–903.

Developed during tenure as Committee Chair:

1. Female age-related fertility decline. Committee Opinion No. 589. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:719–21.

2. Hormone therapy and heart disease. Committee Opinion No. 565. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;121:1407–10.

3. Professional liability and gynecology-only practice. Committee Opinion No. 567. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:186.

4. Solutions for surgical preparation of the vagina. Committee Opinion No. 571. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:718–20.

5. Understanding and using the U.S. Selected Practice Recommendations for Contraceptive Use, 2013. Committee Opinion No. 577. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1132–3.

6. Von Willebrand disease in women. Committee Opinion No. 580. American College of Obstetricians and Gynecologists. Obstet Gyne-col 2013;122:1368–73.

7. Addressing health risks of noncoital sexual activity. Committee Opinion No. 582. American College of Obstetricians and Gynecologists. Obstet Gynecol 2013;122:1378–83.

Editorials and Letters

1. **Clarke-Pearson DL**, Geller EJ. Complications of Hysterectomy. Obstet Gynecol 2013; 121:1-21.

2. **Clarke-Pearson DL**. Thromboprophylaxis in Gynecologic Surgery: Why are we Stuck in 1975? Obstet Gynecol 2011; 118: 973.

3. Martino M, Rajaram L, Maxwell GL, **Clarke-Pearson DL**. Combination Prophylaxis for Thromboembolism Prevention among Gynecologic Oncology Patients Perioperatively. (Letter) Gynecol Oncol 2008; 109: 426-27.

4. **Clarke-Pearson DL**: Prevention of venous thrombosis following gynecologic Surgery. J Gynecol Tech 1(1):11-17, 1995.

5. **Clarke-Pearson DL**: Crafting the operative note: techniques critical to success (editorial). J Gynecol Tech 1(3):119-120, 1995.

6. **Clarke-Pearson, DL**: Reassessment of ovarian cancer: What are our goals? Gynecol Oncol 52:151-153, 1994.

7. Soper JT, **Clarke-Pearson DL**, Berchuck A: The clinical significance of blood transfusion at the time of radical hysterectomy. (Letter). Obstet Gynecol 77:165, 1991.

8. **Clarke-Pearson DL**: The importance of calf vein thrombosis. N Eng J Med 302:752, 1980.

Published Abstracts

1. Barber EL, **Clarke-Pearson DL**. Risk of venous thromboembolism in minimally invasive versus open hysterectomy for endometrial cancer. SGO Annual Meeting 2016.

2. Barber EL, Gehrig PA, **Clarke-Pearson DL**. A risk assessment score for postoperativeVTE among patients undergoing minimally invasive surgery for gynecologic cancer. SGO Annual Meeting 2016.

3. Barber EL, **Clarke-Pearson DL**. Validity of currently available venous thromboembolism risk scores among gynecologic oncology patients.

4. Look K, Brunetto VL, **Clarke-Pearson DL**, Averette H, Major FJ, Alvarez RD, Homesley HD, Zaino R: An analysis of cell type in patients with surgically stages stage IB carcinoma of the cervix: A Gynecologic Oncology Group (GOG) Study. Abstract. Gynecol Oncol 60:117, 1996.

5. Omura GA, Blessing J, Vaccarello L, Berman M, Mutch D, **Clarke-Pearson DL**, Anderson B: A randomized trial of Cisplatin versus Cisplatin + Mitolactol versus Cisplatin + Ifosfamide in advanced squamous carcinoma of the cervix by the Gynecologic Oncology Group (GOG). Abstract. Gynecol Oncol 60:120, 1996.

6. Omura GA, Blessing J, Vaccarello L, Berman M, Mutch D, **Clarke-Pearson DL**, Anderson B: A randomized trial of Cisplatin versus Cisplatin + Mitolactol versus Cisplatin + Ifosfamide in advanced squamous carcinoma of the cervix by the Gynecologic Oncology Group (GOG). Abstract. ASCO, 1995.

7. Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Vogel S, Franklin FW, **Clarke-Pearson** DL, Malviya VK, Dubeshter B, Hoskins W, Adelson M, Alvarez RD, O=Sullivan J, Garcia DJ, Sparks D, Rothenberg ML: Phase III study of intraperitoneal (IP) Cisplatin CDDP)/Intravenous (IV) Cyclophosphamide (CPA) vs. IV CDDP/IV CPA in patients (Pts) with optimal disease stage III ovarian cancer: A SWOG-GOG Intergroup Study. Abstract. ASCO, 1995.

8. Stehman FB, Bundy BN, Ball H, **Clarke-Pearson DL**: Sites of failure and times to failure in carcinoma of the vulva treated conservatively: A Gynecologic Oncology Group Study. Abstract. AGOS 1995.

9. Omura GA, Blessing J, Vaccarello L, Berman M, Mutch D, **Clarke-Pearson D**, Anderson B: A randomized trial of cisplatin versus cisplatin + mitolactol (CM) versus cisplatin + ifosfamide (CIFX) in advanced squamous carcinoma of the cervix (SCC) by the Gynecologic Oncology Group (GOG). Presented at the 1995 American Society of Clinical Oncology Annual Meeting.

10. **Clarke-Pearson DL**, Berchuck A, Kohler M, Rodriguez GC: Retroperitoneal drains/morbidity of nodes. Society of Gynecologic Oncologists, 1993.

11. Hoskins WJ, McGuire WP, Brady MS, Copeland L, Homesley HD, **Clarke-Pearson DL**: Serum CA-125 for prediction of progression in advanced epithelial ovarian carcinoma (AOC). The Gynecologic Oncology Group (GOG). Proc ASOC (Abstract #707) 11:223, March 1992.

12. McGuire WP, Hoskins WJ, Brady MF, Homesley HD, **Clarke-Pearson DL**: A Phase III trial of dose intensive (DI) cisplatin (CDDP) and Cytoxan (CTX) in advanced ovarian cancer (AOC). Proc ASCO, March 1992.

13. Hoskins WJ, McGuire WP, Brady MS, Homesley HD, **Clarke-Pearson DL**: Serum CA-125 for prediction in advanced epithelial ovarian cancer (AOC). The Gynecologic Oncology Group (GOG).

Third Meeting of the International Gynecologic Cancer Society, September 22-26, 1991, Cairns, Australia.

14. McGuire WP, Hoskins WJ, Brady MS, Homesley HD, **Clarke-Pearson DL**: A Phase II trial of dose intense (DI) versus standard dose (SD) Cisplatin (CDDP) and Cytoxan (CTX) in advanced ovarian cancer (AOC). The Gynecologic Oncology Group (GOG). Third Meeting of the International Gynecologic Cancer Society, September 22-26, 1991, Cairns, Australia.

15. Shpall E, **Clarke-Pearson DL**, Soper JT, Berchuck A, Jones R, Bast R, Lider Y, Vanacek K, Tyler T, Peters W: High dose alkylating agent chemotherapy with autologous bone marrow support in patients with Stage III/IV epithelial ovarian cancer. Society of Gynecologic Oncologists, 1990.

16. Soisson AP, Soper JT, Berchuck A, Creasman WT, **Clarke-Pearson DL**: The role of radiation therapy following radical hysterectomy for carcinoma of the cervix. Society of Gynecologic Oncologists, 1989.

17. Berchuck A, Soisson AP, Soper JT, **Clarke-Pearson DL**, McCarty KS Jr, Bast RC Jr:Cellular expression of CA-125 and metastatic potential of endometrial adenocarcinoma. Society of Gynecologic Oncologists, 1989.

18. Soisson AP, Berchuck A, Soper JT, **Clarke-Pearson DL**, Flowers J, Kinney R, McCarty KSJR, Bast RC Jr: TAG-72 expression in benign and malignant endometrium. American College of Obstetricians and Gynecologists, Armed Forces District Meeting, 1988.

19. Christensen C, McCarty KS Jr, Flowers J, Soper JT, McCarty KS Sr, **Clarke-Pearson DL**: Progesterone receptor in ovarian carcinoma: Comparison of biochemical and immunohistochemical techniques. American College of Obstetricians and Gynecologists, Annual Clinical Meeting, 1988.

20. Genkins SM, Sotsman HD, Spritzer CE, Herfkens RJ, Carroll BA, Kadir S, **Clarke-Pearson DL**, Coleman RE: Diagnosis of deep venous thrombosis: Comparison of venography with four noninvasive techniques. The Radiological Society of North America, 1988.

21. Mutch DG, Soper JT, Babcock CJ, Christensen CW, **Clarke-Pearson DL**, Hammond CB: Recurrent gestational neoplasia: Experience of the Southeastern Trophoblastic Disease Center. Abstract, Gynecol Oncol 29:133, 1988.

22. Christensen C, McCarty KS Jr, Flowers J, Soper JT, McCarty KS Sr, **Clarke-Pearson DL**: Analysis of estrogen receptor in ovarian carcinoma using biochemical and monoclonal antibody assays. Presented at American College of Obstetricians and Gynecologists District IV Meeting. Atlanta, Georgia, October 1987.

23. **Clarke-Pearson DL**, Creasman WT: Prevention of postoperative deep venous thrombosis by two intense low-dose heparin regimens: A controlled trial. Abstract, Society of Pelvic Surgeons, 1986.

24. **Clarke-Pearson DL**, DeLong ER, Synan IS, Coleman RE, Creasman WT: Variablesassociated with postoperative deep venous thrombosis. Abstract, Society of Gynecologic Investigation, p. 119, 1986.

25. Siegel RS, Kessler CM, **Clarke-Pearson DL**, Barth S, Fortune W, Reba R, Coleman RE: Application of Indium-111-labeled donor platelets to detection of deep venous thrombosis. Clin Res 32:323A, 1984.

26. Creasman WT, Henderson D, **Clarke-Pearson DL**: Use of estrogens after treatmentfor adenocarcinoma of the endometrium. Gynecol Oncol 17:2, p. 255, 1984.

27. Siegel RS, **Clarke-Pearson DL**, Barth S, Fortune W, Lewis RJ, Reba R, Coleman RE: Application of Indium-111-labeled donor platelets to detection of deep venous thrombosis and monitoring clot

resolution on streptokinase therapy. Blood, Suppl 62:310,1983.

28. Siegel RS, **Clarke-Pearson DL**, Coleman RE: Indium-111-labeled platelets in the detection of deep venous thrombosis and pulmonary embolism. Blood 50:223, 1982.

29. Postoperative thromboembolism prophylaxis in gynecologic oncology: A prospective, controlled trial of low-dose heparin and external pneumatic calf compression. Gynecol Oncol, 1982.

Un-refereed Publications

1. **Clarke-Pearson DL**. Prevention and Management of Venous Thromboembolism (15 minute Video) for the Globathon to End Women's Cancer. September 2014.

2. **Clarke-Pearson DL**, Brincat C, Tang J. Prevention and Management of Venous Thromboembolism in Gynecologic Surgery. ACOG Update. Vol 37, No 2. August, 2011.

3. **Clarke-Pearson DL**. Preventing Venous Thromboembolism: Evidence-based Perioperative tactics. OBG Management. 2006, 18: 56-66.

4. **Clarke-Pearson DL**: Prevention of venous thrombosis following gynecologic surgery in menopausal patients. Menopausal Medicine Vol 4 (4):6-9, 1996.

5. Rodriguez GC, **Clarke-Pearson DL**: What is the appropriate preoperative and prenatal screen for hemostatic disorders? Obstet Gynecol Forum, November 1991.

6. **Clarke-Pearson DL**, Hume RF: Venous thromboembolic disease in obstetrics and gynecology: Prevention, diagnosis and treatment. Curr Problems in Obstet Gynecol, 1989.

7. Hunter VJ, Christensen C, **Clarke-Pearson DL**: Evaluation and management of the abnormal Papanicolaou smear. North Carolina Family Physician, 1989.

8. **Clarke-Pearson DL**, Krumholz AB: When the pap smear is equivocal. Patient Care 23:43-47, 1989.

9. **Clarke-Pearson D**, DiSaia P, Mastroianni L, Richart R, Weingold AB: Advances in managing endometrial carcinoma. Patient Care 22:102-116, 1988.

10. Creasman WT, Smith EB, **Clarke-Pearson DL**: Current concepts of gestational trophoblastic disease. Female Patient, 1984.

11. Creasman WT, **Clarke-Pearson DL**: Abnormal cervical cytology: Spotting it, treating it. Contemporary Obstet Gynecol 21:53-76, 1983.

12. Hammond CB, **Clarke-Pearson DL**, Soper JT: Management of patients with gestational trophoblastic neoplasia: Experience of the Southeastern Regional Center. In: The Proceedings of the World Congress on Gestational Trophoblastic Neoplasia, Nigeria, 1982.

13. **Clarke-Pearson DL**: Application of impedance phlebography in obstetrics. Symposium on Noninvasive Diagnostic Techniques in Vascular Disease. San Diego, California, 1979.

14. **Clarke-Pearson DL**: The O.S.R. as an influence to health education. The Scalpel, Journal of Alpha Delta Alpha Medical Honor Society, 1975.

Teaching Record

2022 Society of Pelvic Surgeons Annual Meeting: Panel Moderator- "Where are the limits to cancer excision and reconstruction?"

2020 George Washington University Medical Oncology Board Review Course (Faculty) "Cervix, vulva vagina cancer and gestational trophobalastic disease" (by zoom)

2019 Presidential Speaker, South Atlantic Association of ObGyn Annual meeting, Sea Island Georgia

George Washington University Medical Oncology Board Review Course (Faculty) "Cervix, vulva vagina cancer and gestational trophobalastic disease"

2018 Visiting Professor, University of West Virginia, Morganton, WVa
Antonio Palladino Lectureship

George Washington University Medical Oncology Board Review Course (Faculty) "Cervix, vulva vagina cancer and gestational trophobalastic disease"

2016 Plenary Session, Society of Pelvic Surgeons, St Louis, Mo. "Venous Thromboembolism:

Minimally Invasive Compared with Open Hysterectomy for Endometrial Cancer"
Key Note Speaker. ACOG Armed Forces District Meeting, Orlando, FL

Visiting Professor and Research Day Judge, Cleveland Clinic Department of Obstetrics and Gynecology and Women's Research Institute, Cleveland, Ohio

Visiting Professor, Department of Obstetrics and Gynecology, Carilion Roanoke Memorial Hospital, Roanoke, Va.

George Washington University
Medical Oncology Board Review Course (Faculty) "Cervix, vulva vagina cancer and gestational trophobalastic disease"

2015 Visiting Professor
University of Michigan

George Washington University
Medical Oncology Board Review Course (Faculty)

2014 Visiting Professor
Massachusetts General Hospital, ObGyn Department Grand Rounds Boston, MA
Invited speaker: ACOG District II Annual Meeting, New York City "Uterine Morcellation: A Decision Analysis"

George Washington University Medical Oncology Board Review Course (Faculty) "Cervix, vulva vagina cancer and gestational trophobalastic disease"

2013 Visiting Professor and Resident Research Day Judge
Department of Obstetrics and Gynecology, University of Nebraska Omaha, NE
Visiting Professor, Emory University Department of Obstetrics and Gynecology Atlanta, GA

Key Note Speaker: Inaugural Ireland Ovarian Cancer Forum "Surgery for Ovarian Cancer"
Dublin, Ireland

Panel Moderator, American College of Surgeons Annual Clinical Congress "General Surgery in the Pregnant Patient" Washington, DC

George Washington University
Medical Oncology Board Review Course (Faculty)

2012 Clifford Wheless Lectureship, Johns Hopkins University, Department of Obstetrics and Gynecology, Baltimore, MD

Panel Moderator, American College of Surgeons Annual Clinical Congress "Multidiciplinary approach

to Vaginal Fistula" Chicago, IL

Resident Research Day Judge and Visiting Professor
Department of Obstetrics and Gynecology, Greenville Hospital System, Greenville, SC

Visiting Professor: University Teaching Hospital, Department of Obstetrics and Gynecology, Lusaka, Zambia

Cervical Cancer management
Current Treatment of Vulvar Carcinoma

Visiting Professor: Center for Infectious Disease Research in Zambia (CIDRZ), Lusaka, Zambia

Human Papilloma Vaccine for the Prevention of Cervical Cancer

Visiting Professor: Inova Fairfax Hospital Women's Center, Fairfax VA

Visiting Professor: Emory University School of Medicine, Department of Obstetrics and Gynecology. Atlanta, GA

George Washington University
Medical Oncology Board Review Course (Faculty)

2011 Sloane Symposium: Current Issues and Controversies in Obstetrics and Gynecology Columbia University, College of Physicians and Surgeons, Department of Obstetrics and Gynecology
Vandewiele Lecturer: "Prevention of Venous Thromboembolism in Gynecologic Surgery"
Guest Lecturer and Judge: Resident Research Day, Columbia University "What to say in your Operative Note"

University of Kentucky: Residents' Research Day Speaker
Virginia Commonwealth University School of Medicine. Department of Obstetrics and Gynecology
Annual Ware-Dunn Symposium Keynote speaker

George Washington University
Medical Oncology Board Review Course (Faculty)

2010 New England Obstetrical and Gynecological Society, Sturbridge, MA
Invited Speaker

ACOG Annual Clinical Meeting, San Francisco, CA
Luncheon Seminar Leader

George Washington University Medical Oncology Review Course
Washington, DC
Invited Faculty

MD Anderson Cancer Center Medical Oncology Review Course
Houston, TX
Invited Faculty

The Society of Gynecologic Oncology of Canada
Royal College of Physicians and Surgeons of Canada
Annual Meeting
Invited Lecturer: Thromboprophylaxis in Minimially Invasive Surgery

Visiting Professor
University of South Florida, Tampa, FL
2009 Resident Research Day

ACOG District IV Meeting, Asheville, NC
"Prevention of Venous Thromboembolism"
"Stump the Professors: Panel"

American College of Surgeons' Annual Meeting, Chicago, IL
"Complicated Hysterectomy"

Visiting Professor: Hartford Hospital, Hartford CT

Visiting Professor: University of Connecticut, Farmington, CT

Visiting Professor: Memorial Sloan Kettering Cancer Center

Southern Obstetric and Gynecologic Seminar, Asheville, NC
"Prevention of VTE following Gynecologic Surgery"
"The Operative Note: What to say?"

Woman's Hospital 7th Annual Founders Commerative Lectureship, Woman's Hospital, Baton Rouge, LA

2008 Visiting Professor, Department of Obstetrics and Gynecology, Yale University

Course Director, ACOG CME Course "Complex Pelvic Surgery", Phoenix, AZ

Invited Speaker: First Annual Gynecologic Cancer Symposium, Washington, DC April 18, 2008

Visiting Professor, University of Wisconsin Resident's Research Day, Ben M. Peckman Memorial Lecturer, Madison, WI

ACOG representative to Symposium on Surveillance for Venous Thrombosis, American Society of Hematology, Washington DC

2007 Visiting Professor, Department of Obstetrics and Gynecology, University of Miami

Faculty, University of Utah CME Course "Obstetrics and Gynecology: Update and Current Controversies" Park City Utah

Visiting Professor, Department of Obstetrics and Gynecology St. Louis University, St. Louis MO

Invited Lecturer: Marvin Camel Memorial Lecture, Washington University, Department of Obstetrics and Gynecology, St Louis, MO

Presidential Panel Speaker: Society of Pelvic Surgeons Annual Meeting, Cleveland, OH "What Can We do to prevent Venous Thromboembolism?"

2006 Course Director: ACOG Annual Clinical Meeting: "Complex Gynecologic Surgery, Washington DC

Invited Speaker, ACOG District IV Annual Meeting, Palm Beach, FL

2005 Course Director: ACOG Annual Clinical Meeting: "Complex Gynecologic Surgery, San Francisco

Course Director: ACOG Free-standing CME Course "Complex Gynecologic Surgery, Preventing Complications" Dana Point, CA

2004 Society of Surgical Oncology: Symposium on Prevention of Venous Thromboembolism in the Surgical Oncology Patient

Postgraduate Course Faculty: ACOG Cancun, Mexico "Advanced Gynecologic Surgery"

American College of Obstetricians and Gynecologists, Annual Clinical Meeting, Philadelphia, PA
Faculty, 120 Course: Special Topics for the Advanced Gynecologic Surgeon
Faculty, Luncheon Seminar: "Prevention of Postoperative Venous Thromboembolism"
Speaker: "Late-breaking News in Gynecologic Oncology"

Visiting Professor, University of Kansas School of Medicine, Truman Medical Center

Faculty: ACOG Indiana Section Meeting, Indianapolis
"Surgery in the Obese Patient", "Surgical Instruments"

2003 Faculty, The 3rd Annual Cancer Conference, Aultman Cancer Center, Canton Ohio "Prevention and Management of Perioperative Venous Thromboembolism in the Gynecologic Cancer Patient"

Visiting Professor, Department of Obstetrics and Gynecology, University of Massachusetts, Worcester, MA

2002 Visiting Professor
Bowman Gray School of Medicine

Residents' Day Research Judge
Winston Salem, NC

American College of Surgeons' Annual Clinical Congress
Panel Discussant: "Surgical Problems: Unexpected adenxal mass, tuboovarian abscess"
Video Presentation: "Intraoperative Radiation Therapy for the treatment of Recurrent Cervical Carcinoma"
Discussant: Video Presentation "Laparoscopic Infrarenal paraarotic lymphadenectomy"

2001 ACOG Annual Meeting
Postgraduate Seminar
Gynecologic Surgery in the Elderly

George Washington University
Medical Oncology Board Review Course (Faculty)

2000 Keynote Speaker
Knoxville Obstetrical and Gynecological Society

ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon

Visiting Professor
East Carolina University School of Medicine

Visiting Professor
Pennsylvania State University School of Medicine (Hershey)

George Washington University
Medical Oncology Board Review Course (Faculty)

1999 ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon

George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)

Visiting Professor
University of Virginia Health Sciences Center

ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon

1998 ACOG Annual Meeting (Course Director)
Postgraduate Course
Gynecologic Surgery for the Advanced Pelvic Surgeon

George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)

Visiting Professor
Temple University School of Medicine

Keynote Speaker
Maryland Obstetrical and Gynecological Society

Visiting Professor
University of Louisville
"Prevention of Postoperative Venous Thromboembolism"
"Management of Patients with Thrombophilias"

1997 Visiting Professor
University of Utah, Salt Lake City

ACOG Annual Meeting (Course Director)
Postgraduate Course
Advanced Surgery for the Gynecologist

Visiting Professor
Cleveland Clinic Foundation
Department of Obstetrics and Gynecology
Cleveland, Ohio

George Washington University School of Medicine
Medical Oncology Board Review Course (Faculty)

Keynote Speaker
Chicago Gynecological Society

Visiting Professor
University of Louisville School of Medicine

Visiting Professor
Washington University School of Medicine

Visiting Professor
Johns Hopkins University School of Medicine

ACOG Annual Clinical Meeting
Faculty, 120 Course: Special Topics for the Advanced Gynecologic Surgeon
Faculty, Seminar: "Gynecologic Surgery in the Elderly"
Faculty, Luncheon Seminar: "Prevention of Postoperative Venous Thromboembolism"

American College of Surgeons' Annual Clinical Congress
Panel Discussant: "Management of Gynecologic Problems Encountered by the General Surgeon at the time of Surgery. "Surgical Management of Ovarian Cancer Discovered at the time of Laparotomy"

1996 Visiting Professor
Dartmouth Medical School

Director ACOG Postgraduate Course
Annual Clinical Meeting

Special Problems for the Advanced Gynecologic Surgeon

Visiting Professor
University of Tennessee School of Medicine
Chattanooga, Tennessee

Visiting Professor
University of South Florida School of Medicine
Tampa, Florida

Visiting Professor
Washington University School of Medicine
St. Louis, Missouri

John L. McKelvey Lecturer
New Treatments for Ovarian Cancer
University of Minnesota
Minneapolis, Minnesota

Faculty - Taubman Ovarian Cancer Symposium
St. Joseph's Hospital
Tulsa, Oklahoma

ACOG Postgraduate Course (Course Director)
San Juan, Puerto Rico
Advanced Pelvic Surgery

1994 ACOG Clinical Meeting CME Course
Orlando, FL
"Gynecologic Cancer"

Guest Speaker
Seattle Gynecological Society Assembly

1993 Visiting Professor - Department of OB/GYN
University of Massachusetts
Worcester, Massachusetts

ACOG Clinical Meeting - CME Course
Washington, DC
"Gynecologic Surgery"

PostGraduate Course in Obstetrics and Gynecology
Kaiser-Permanente - Maui, Hawaii
"Screening for Ovarian Cancer"
"Management of CIN with LEEP"
"Difficult Vaginal Hysterectomy"
"Incisions and Wound Closures"

Duke/US Surgical Course
"Laparoscopic Assisted Difficult Hysterectomy"

Visiting Professor - Mt. Sinai Hospital
Baltimore, MD
"Prevention of Thromboembolism"
"Management of Ovarian Cancer"

1992 Visiting Professor - Department of OB/GYN
University of Massachusetts
Worcester, Massachusetts

1991 Visiting Professor
George Washington University School of Medicine

Course Director - ACOG Course (120 series)
Annual Clinical Meeting
New Orleans, Louisiana
"Gynecologic Oncology for the Practicing Gynecologist"

Course Director - ACOG Course
Vancouver, British Columbia, Canada
"Gynecologic Surgery"

Visiting Professor
Florida Hospital Cancer Center
Orlando, Florida

Paper Presentation
Poster Presentation
Society of Gynecologic Oncologists
Orlando, Florida

Visiting Professor
Ohio State University School of Medicine
Columbus, Ohio

Medical Oncology Board Review Course
George Washington University
Washington, DC
"Cervical, Vulvar and Vaginal Cancer"
"Gestational Trophoblastic Disease"

1990 Society of Gynecologic Oncologists
Breakfast Seminar
"Diagnosis and Prevention of Postoperative Venous Thrombosis"

Course Director - ACOG Course (120 Series)
Annual Clinical Meeting
San Francisco, California
"Update in Clinical Gynecologic Oncology"

Seminar, ACOG Clinical Meeting
"Prevention of Postoperative Venous Thrombosis"

1989 Tumor Conference, Moore Regional Hospital
Pinehurst, North Carolina

Course Director - ACOG Course (120 Series) Annual Clinical Meeting, Atlanta, Georgia
"Update in Clinical Gynecologic Oncology"

Seminar, ACOG Clinical Meeting
"Management of Early Ovarian Cancer"

Luncheon Conference, ACOG Annual Meeting
"Reproductive Outcome Following Cancer Treatment"

Medical Oncology Board Review Course, George Washington University, Washington, DC
"Cervical Cancer"

1988 Matt Weiss Symposium
St. Louis, Missouri

ACOG Annual Clinical Meeting
Poster Session Presentation
Review of Clinical Research Paper
Review of Surgical Film
Clinical Seminar Presentation

ACOG Course
Juneau, Alaska
"Gynecologic Surgery"

1987 Update in Obstetrics and Gynecology
Williamsburg, Virginia

North Carolina Obstetrical and Gynecological
Society Meeting, Southern Pines, North Carolina

Visiting Professor, University of Minnesota School of Medicine, Minneapolis, Minnesota

ACOG Annual Clinical Meeting
Clinical Paper Presentation
Clinical Seminar Presentation

Southern Obstetrics and Gynecology Seminar
Asheville, North Carolina

Satellite Teleconference
Chicago, Illinois
"Selected aspects of the care of the menopausal woman"

Chicago Medical Schools' Review Course
Chicago, Illinois
"Endometrial Carcinoma"

Grants

Active Grants:					
None at this time					
Completed Grants:					

Project Period	Agency	Title	Amount	Role	% of Effort
9/27/05-3/10/10	NIH/NICHD	Women's Reproductive Health Research (WRHR) Career Development Center at UNC - HDD050113-02	$370,367 Annual Direct Costs	Principal Investigator	
3/1/00-3/31/02	Pharmacia Upjohn Pharmaceuticals	Randomized Comparison of Low Molecular Weight Heparin vs. Oral Anticoagulant Therapy for Long Term Anticoagulation in cancer patients – 98-Frag-069	$ 73,000	Principal Investigator	
1/1/99-6/15/00	Zeneca Pharmaceuticals , Inc	Phase II/III Trial of IV ZD9331 in patients with recurrent refractory ovarian cancer	$ 18,320	Principal Investigator	
6/1/98-6/1/00	Pharmacia Upjohn Pharmaceuticals	Prospective Randomized Trial Comparing Pneumatic Compression stockings To Low Molecular Weight Heparin (dalteparin) in the prevention of postoperativevenous Thrombosis	$ 100,760	Principal Investigator	
06/01/95 - 05/31/2000	National Cancer Institute	Hyperthermia and Perfusion Effects in Cancer Therapy	$10,930,969	Investigator	2%
03/15/98- 03/14/00	Novartis Pharmaceuticals	PSC 833 with taxol and carboplatin vs. carboplatin alone in patients with stage III ovarian cancer	$ 102,240	Principal Investigator	
8/1/97-7/31/99	NIH	Hyperthermia and Perfusion Effects in Cancer Therapy	$ 1,832,501	Co-Investigator	
5/28/97-12/31/98	Smithkline Beecham Pharmaceuticals	Oral Topotecan Single Agent for 5 days in patients with ovarian cancer	$ 81, 600	Principal Investigator	
01/01/93- 12/31/98	National Cancer Institute	Comprehensive Cancer Center Core Support Grant	$ 4,442,597	Program Director	10%
06/01/94 -	National Cancer	Autologous Bone	$641,613	Investigator	10%

03/31/97	Institute	Marrow Transplantation in Breast and Ovarian Cancer: Project IB			
03/15/96-05/30/96	Ethicon, Inc	An Open, Controlled, Rand, Multicenter, Evaluation of Dyed Monocryl (Poliglecaprone 25) Synthetic Absorbable Suture as Compared to Surgical Gut (Chromic) Absorbable Suture	$ 4,000	Principal Investigator	
1987-1996	American Cancer Society	Clinical Oncology Fellowship	$ 20,000 (Direct)	Principal Investigator	5%
10/01/92-09/30/94	Centocor, Inc.	CA125 Post-Market Evaluation	$ 8,750	Principal Investigator	5%
12/15/93-09/21/94	Smith-Kline Beecham Pharmaceutical	Phase III Topotecan versus Taxol in Women with Advanced Ovarian Carcinoma	$ 37,500	Principal Investigator	5%
12/15/93-08/14/94	Smith-Kline Beecham Pharmaceutical	II Topotecan, Given as Five Daily Doses Every 21 Days in Ovarian Cancer	$ 37,500	Principal Investigator	10%
07/01/89 - 03/31/94	Gynecologic Oncology Group	Gynecologic Oncology Group, Duke University Medical Center	$ Contingent on number of patients	Co-Principal Investigator	30%
01/01/91 – 09/01/93	Organon, Inc.	ORG 2766 as a Neuroprotector from Cisplatin Chemotherapy for Ovarian Cancer	$97, 575	Principal Investigator	10%
02/01/91 - 01/31/92	Organon, Inc.	Decapeptyl Treatment of Advanced Ovarian Cancer (Phase II Trial)	$100,098	Principal Investigator	10%
11/01/90-10/31/91	Cytogen, Inc.	111In-CYT-103 Oncoprobe Evaluation of Ovarian Cancer	$ 124,000	Principal Investigator	10%
07/01/86-06/30/91	National Institutes of Health	Avoidable Mortality from Cancers in Black Populations	$ 4,647,291	Co-Investigator	10%
06/01/87 - 05/31/89	Public Health Service	Improved Instrumentation for the Diagnosis of Venous Thrombosis	$162,804 (Direct)	Co-Principal Investigator	10%
05/01/88 -	National Cancer	Gynecologic	$97,073	Co-Principal	10%

04/30/89	Institute	Oncology Group, Duke University Medical Center	(Direct)	Investigator	
01/01/88 - 12/30/88	Centocor, Inc.	Evaluation of the Safety and Preliminary Diagnostic Accuracy of IV Administered Indium-111-labeled OC-125 Monoclonal Antibody in Patients with Carcinoma of the Ovary	$ 20,000 (Direct)	Co-Principal Investigator	5%
01/01/88 - 12/30/88	Centocor, Inc.	Evaluation of the Safety and Preliminary Diagnostic Accuracy of IV Administered Indium-111-labeled OV-TL3 Monoclonal Antibody in Patients with Carcinoma of the Ovary	$ 40,000 (Direct)	Co-Principal Investigator	5%
05/01/85- 04/30/87	National Cancer Insitute	Illinois Cancer Council - Gynecologic Oncology Group	$ 21,000 (Direct)	Co-Principal Investigator	10%
07/01/81- 06/30/84	American Cancer Society	Junior Faculty Clinical Fellowship	$ 35,000	Principal Investigator	30%
01/01/83- 12/31/83	Trent Foundation	In-vitro chemotherapy sensitivity testing of ovarian carcinoma	$ 1,000	Principal Investigator	5%

PROFESSIONAL SERVICE

To discipline:

A. National/International

2023 President Elect, Society of Pelvic Surgeons

2021- 2022 Chair, NRG Oncology Data Monitoring Committee (Gynecologic Oncology Group)

2019-2023 Vice President, Society of Pelvic Surgeons
Editorial board member: Journal of Gynecologic Surgery

2018-2020 Chair, Council of University Chairs of Obstetrics and Gynecology

2014 Chair, External Site Visit Committee, Department of Obstetrics and Gynecology, Penn State
2014 University College of Medicine, Department of Obstetrics and Gynecology Member,
2014 CUCOG Executive Board

2011 Member, American College of Surgeons Advisory Committee (ObGyn)
2011 Member, CUCOG Executive Committee
2011 Chair, ACOG Committee on Gynecologic Practice
2011 Chair, SGO Nominating Committee

2010-2013 Immediate Past President, SGO
2010-2013 Member, ACOG Executive Board (Representing the Society of Gynecologic Oncology)
2011-2013 Chair, Committee on Gynecologic Practice, ACOG
2007 -2010 Member, Education/Research Committee, Society of Pelvic Surgeons
1988- 2005 Board Examiner: Obstetrics and Gynecology , ABOG
2010-2011 Vice-Chair, Committee on Gynecologic Practice, ACOG
2010 President, Society of Gynecologic Oncologists
2009-2010 Editorial Board, Precis, Gynecology, ACOG
Program Chair, Society of Pelvic Surgeons

2008
2008-2010 Committee on Gynecologic Practice, ACOG
2008 President Elect II, Society of Gynecologic Oncologists
2008 Chair, Membership Committee. Society of Pelvic Surgeons
2007-2008 Vice President, Society of Gynecologic Oncologists

2007
2007 Editorial Board: Precis, Oncology, ACOG
2007 SGO Executive Council, Society of Gynecologic Oncologists
2007 Chair, Task Force to select Editor and Chief, *Gynecologic Oncology,* Society of Gynecologic Oncologists
2007 Co-Chair, Strategic Planning Committee, Society of Gynecologic Oncologists
2007 Member, By-laws Committee, Society of Gynecologic Oncologists

2005
2005 NC Breast and Cervical Cancer Control Program's (BCCCP) Medical Advisory Committee, North Carolina Department of Environment, Health, and Natural Resources
2005-2019 Member, Clinical Cancer Committee, Moses Cone Health System
2005-2019 Director, Gynecologic Oncology Program, Moses Cone Health System
2005-2019 Member, Cancer Center Executive Committee, Moses Cone Health System
1998-2005 Member, Executive Committee Cancer Center Clinical Service Unit, Duke University
1998-2005 Co-Medical Director, Surgical Oncology Clinic, Duke University
1992-2005 Member, Operating Room Committee, Duke University
1991-2005 Principal Investigator, Duke University, Gynecologic Oncology Group
1987-2005 Director of Gynecologic Oncology Fellowship Program (Duke Univ), ABOG
1987-2005 Director, Gynecologic Oncology Program, Duke Comprehensive Cancer Center, Duke University
1987-2005 Member, Steering Committee Strategic Planning Task Force, Duke Comprehensive Cancer Center, Duke University
1987-2005 Member, Executive Committee, Duke Comprehensive Cancer Center, Duke University

2003
2003 Nominating Committee, Society of Gynecologic Oncologists
2003 President and Program Chairman, Mid Atlantic Gynecologic Oncology Society

2002

2002 President-Elect, Mid Atlantic Gynecologic Oncology Society
2002 Member, Membership Committee, Society of Pelvic Surgeons
2002 Member, Oncology Strategic Planning Council, Duke University

2001

2001 Editorial Board: Precis, Oncology, ACOG
2001 Board Examiner: Gynecologic Oncology, ABOG

2000

2000 Member, Nominating Committee (AGOS Foundation)
2000 Program Chairman (Annual Meeting), Mid Atlantic Gynecologic Oncology Society
1994-2000 Member, Education Committee, Society of Gynecologic Oncologists

1999

1996-1999 Member, Fellowship Committee, AGOS

1998

1994-1998 Council Member, Society of Gynecologic Oncologists
1990-1998 Ovarian Cancer Committee, Gynecologic Oncology Group

1997

1993-1997 Editorial Board Member, Duke Cancer Report, Duke University
1993-1997 Committee on Gynecologic Practice, ACOG
1993-1997 Chairman, Committee on Gynecologic Oncology Practice, ACOG
1993-1997 ACOG Liaison Representative to the Society of Gynecologic Oncologists
1994-1997 Member, Committee on Clinical Practice, Society of Gynecologic Oncologists

1995

1994-1995 Chairman, 1995 Program Committee, Society of Gynecologic Oncologists

1994

1993-1994 Ad hoc Council Member, Society of Gynecologic Oncologists
1993-1994 Ad hoc Committee on Clinical Practice Policy Development Society of Gynecologic Oncologists
1994 Society of Pelvic Surgeons

1993

1991-1993 Chairman, Gynecology Committee, North Carolina OB/GYN Society
1991-1993 Member, Professional Activities Committee, North Carolina OB/GYN Society
1993 Medical Director, Duke North Hospital, 5900 Unit, Duke University
1993 Fellow, American Gynecological and Obstetrical Society
1993 Member, Ad hoc Committee to Define Criteria for Tenure in Clinical Medicine , Duke University
1993 Department of Surgery Chairman Search Committee, Duke University

1992

1990-1992 Member, Task Force on Cervical Cancer, Chairman, Subcommittee on Impact of Appropriate Follow-up Care, North Carolina Department of Environment, Health, and Natural Resources

1991

1987-1991 Co-Principal Investigator, Duke University Grant, Gynecologic Oncology Group
1987-1991 Committee on Technical Bulletins, ACOG
1991 Board Examiner: Gynecologic Oncology, ABOG
1991 Member, Director of Surgical Pathology Search Committee, Duke University

1990

1990 Member, Department of Pathology Chairman Search Committee, Duke University
1982-1990 Gynecologic Management Committee, Gynecologic Oncology Group

1989

1989 Fellow, American College of Surgeons

1988

1988 Mid-Atlantic Gynecologic Oncology Society
1988 Southern Obstetrical and Gynecological Seminar
1988 International Gynecologic Cancer Society
1988 Mid-Atlantic Gynecologic Oncology Society
1988 Southern Obstetrical and Gynecological Seminar

1987

1985-1987 Chicago Medical Society
1985-1987 Illinois Cancer Council
1985-1987 Illinois State Medical Society
1985-1987 Chicago Association of Gynecologic Oncologists
1987 North Carolina Medical Society
1987 North Carolina Obstetrical and Gynecological Society
1987 American Society of Clinical Oncologists

1986

1986 Chicago Gynecological Society

1985

1982-1985 Co-Principal Investigator, Duke University Grant, Gynecologic Oncology Group
1985 Central Association of Obstetricians and Gynecologists
1985 Central Association of Obstetricians and Gynecologists
1985 American Medical Association

1982

1982 Gynecologic Oncology Group
1982 Society of Gynecologic Oncologists
1982 Fellow, American College of Obstetricians and Gynecologists

1979

1979 Piedmont Obstetrical and Gynecological Society
1979 Bayard Carter Society of Obstetricians and Gynecologists
1979 Junior Fellow Section Chairman, ACOG

1978

1978 Junior Fellow Section Co-Chairman, ACOG

1977

1977 Junior Fellow Section Program Chairman, ACOG

B. Within UNC-Chapel Hill

2018-2021 Member, School of Medicine Promotions and Tenure Committee
2013-2019 Member, UNC Hospitals Committee of Perioperative Leaders
2011-2019 Member, Physicians and Associates Executive Committee
Member, P&A Finance and Compensation Committee
Member, P&A Committee on Payer Relations

2009- Member, Strategic Planning Committee: Hillsboro Hospital
2009-2019 Member, Strategic Planning Committee UNC HCS
2008-2019 Member, Dean's Advisory Committee on Part-Time Tenure Track Positions 2008-present Member Geographic Strategic Planning Committee
2008- 2019 Member UNC Strategic Planning Committee: Outpatient Surgery 2008-present Member UNC Strategic Planning Committee: Oncology
2007-2019 Member, Sheps Center Advisory Board
2007-2019 Member, Center for Women's Health Research Advisory Board
2007-2009 Team Leader (Attending Physicians' Experience) UNC Hospital Commitment to Caring 2006-present Medical Director, NC Women's Hospital Ambulatory Services
2005-2019 Dean's Advisory Committee
2005-2019 UNC Hospital Executive Committee
2005-2019 Physician and Chief, North Carolina Women's Hospital
2005-2019 Member, Physician and Associates Board/Faculty Physicians
2005-present Member, UNC Lineberger Cancer Center
2006, 2007 Chair, Data Safety Monitoring Board: An International Multi-Center Phase III Study of Chemoradiotherapy versus chemoratiotherapy plusvhyperthermia for locally advanced cervical

Editorial Board Member

1994-2004 Postgraduate Obstetrics and Gynecology
2003 Précis, Oncology, Second Edition
1995-2001 Associate Editor, Journal of Gynecologic Techniques
1994-2000 Gynecologic Oncology
2012-2015 Obstetrics and Gynecology
2020-present Journal of Gynecologic Surgery

Journal Reviewer

Obstetrics and Gynecology

New England Journal of Medicine

American Journal of Obstetrics and Gynecology Journal of the American Medical Association (JAMA)

Annals of Internal Medicine

Pharmacotherapy

Fertility and Sterility

Gynecologic Oncology Cancer

International Journal of Gynecology and Obstetrics Journal of Pelvic Surgery

Journal of Gynecologic Surgery

Exhibit B

Daniel Clarke-Pearson, M.D.
Materials Considered

1. "A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis." *British Journal of Diseases of the Chest* 73 (1979): 285–88.
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3. Acheson, E D, M J Gardner, E C Pippard, and L P Grime. "Mortality of Two Groups of Women Who Manufactured Gas Masks from Chrysotile and Crocidolite Asbestos: A 40-Year Follow-Up." *British Journal of Industrial Medicine* 39, no. 4 (November 1982): 344–48.
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12. "ATSDR - Toxicological Profile: Silica." Accessed August 16, 2018.
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Pulmonary Toxicity of Talc and Granite Dust as Estimated from an in Vivo Hamster Bioassay." *Toxicology and Applied Pharmacology* 87, no. 2 (February 1987): 222–34.

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Company Documents

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99. JNJMX68_000012858
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101. JNJMX68_000013945
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103. JNJNL61_000079334
104. LUZ013094/P-26
105. P-321
106. P-47
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108. PCPC0075758
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111. Pltf_MISC_00000272 (JANSSEN-000001-19) 1962.
112. RA00461
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115. RA00471-72
116. RA00473
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Other Materials

3rd Supplemental MDL Report of William Longo, PhD – Analysis of Non-Historical J&J's Talcum Powder Consumer Product Containers and J&J Chinese Historical Talc Retain Samples, dated November 17, 2023.

William E. Longo, PhD – MDL Johnson's Baby Powder Application and Exposure Container Calculations for Six Ovarian Cancer Victims Bellwether Cases, dated November 17, 2023.

Amended Expert Report of Shawn Levy, PhD, dated November 15, 2023.

Case-Specific Depositions

Deposition of Tamara Newsome, dated 12/09/2020
Deposition of Dr. Albert Steren, dated 02/17/2021
Deposition of Dr. Ravin Garg, dated 02/04/2021
Deposition of Daniel Francois, Jr., dated 05/13/2021
Deposition of Tae'lor Francois, dated 05/14/2021
Deposition of Daniel L. Clarke-Pearson, M.D., dated 08/26/2021
Deposition of Daniel L. Clarke-Pearson, M.D., dated 8/27/2021

Plaintiff Profile Form

Plaintiff Profile Form
First Amended Plaintiff Profile Form
Second Amended Plaintiff Profile Form
Third Amended Plaintiff Profile Form

Medical Records (Defense)

Adventist HealthCare NewsomeT-AdventistHealthcareMR-00001-00004
Adventist HealthCare NewsomeT-WOMCMR-00006-00088
Adventist HealthCare NewsomeT-WOMCMR-00089-00092
Adventist HealthCare NewsomeT-WOMCRad-00001
Adventist HealthCare NewsomeT-WOMCRad-00002-00003
Adventist HealthCare NewsomeT-WOMCRad-00004-00007
Adventist HealthCare NewsomeT-WOMCRad-00008
Adventist HealthCare NewsomeT-WOMCRad-00009
Adventist HealthCare Wash Adventist Hosp NewsomeT-WAHMRPharm-00001-00005
Adventist HealthCare Wash Adventist Hosp NewsomeT-WAHMRPharm-00006-00020
Adventist HealthCare Washington Adventist Hosp NewsomeT-WAHMR-00001-00005
Adventist HealthCare Washington Adventist Hosp NewsomeT-WAHMR-00006-00080
Adventist HealthCare Washington Adventist Hosp NewsomeT-WAHMR-00081-00095
Adventist HealthCare Washington Adventist HospNewsomeT-WAHMR-00001-00075
Adventist HealthCare Washington Adventist Hosp NewsomeT-WAHRad-00001-00004
Annapolis Oncology Ctr NewsomeT-AOCMR-00001-00280
Anne Arundel Med Ctr NewsomeT-AAMC-00001-00008
Anne Arundel Med Ctr NewsomeT-AAMC-00009-00010
Anne Arundel Med Ctr NewsomeT-AAMCMR-00001-00005
Anne Arundel Med Ctr NewsomeT-AAMCMR-00006-00493
Anne Arundel Med Ctr NewsomeT-AAMCRad-00001-00005
Anne Arundel Med Ctr NewsomeT-AAMCRad-00006-00012
Anne Arundel Med Ctr NewsomeT-AAMCRad-00013-00018
Anne Arundel Med Ctr NewsomeT-AAMCRad-00019-00020
Anne Arundel Med Ctr Oncology & Hematology NewsomeT-AAMCOH-00001-00006

Anne Arundel Med Ctr Oncology & Hematology NewsomeT-AAMCOH-00007-00327
Capital Women's Care NewsomeT-CWCMR-00001-00103
Community Radiology Assoc NewsomeT-CRAMR- 00001-00011
Holy Cross Hosp NewsomeT-HCHMR-00001-405
Holy Cross Hospital NewsomeT-HolyCrossH-00001-00011
Holy Cross Hospital NewsomeT-HolyCrossHospPath- 00001
Physicians Inpatient Care Specialists LLC NewSomeT-PICSLLCPB-00001-00004
Quest Diagnostics NewsomeT-QDB-00004-00058
Quest Diagnostics NewsomeT-QDB-00059-00146
Quest Diagnostic Nichols Institute NewsomeT-QDNISJC- 00001-00004
Radiology Holy Cross Hosp NewsomeT-HCHRad-00001-00014
Target Corporation NewsomeT-TPCO-00001-00006
Women's Health Spec. of Montgomery Co. NewsomeT-WHSMCLMR- 00020-00024
Women's Health Spec. of Montgomery Co. NewsomeT-WHSMCLMR- 00025-00098
Women's Health Spec. of Montgomery Co. NewsomeT-WHSMR-00001-00006
Women's Health Spec. of Montgomery Co. NewsomeT-WHSMR- 00007-00020
Women's Health Spec of Montgomery Co. NewsomeT-WHSMCLPB- 00001-00019

Medical Records (Plaintiff)

Anne Arundel Med Ctr NEWSOMET_AAMC_C_MDR000001-410
Anne Arundel Med Ctr Oncology & Hematology NEWSOMET_GARG_C_MDR000003-101
Blasingame, Burch, Garrard & Ashley, PC NEWSOMET REC 00001-00010
Capital Women's Care NEWSOMET_CAPI_MDR000001-000023
Capital Women's Care NEWSOMET CAPI C MDR 00001-00100
Holy Cross Hospital NewsomeT-HCHMR-00406-00422
Holy Cross Hospital NEWSOMET__HCH__MDR000001-000043
Holy Cross Hospital NewsomeT-HolyCrossHospPath-00008-00113
Maryland Oncology Hematology NEWSOMET_MOHA_MDR000001-2
Garg, Ravin NEWSOMET GARG C MDR 00001-00101
Garg, Ravin NEWSOMET GARG MDR 00001-00076
Garg, Ravin NEWSOMET_GARG_C_MDR000001-000002
Maryland Oncology Hematology - Annapolis NEWSOMET_MOHA_C_MDR000001-000003
Maryland Oncology Hematology - Annapolis NEWSOMET MOHA MDR 00001-00002
Muttath, Sureshkumar, M.D. NEWSOMET_MUTTATH_MDR000001-000080
Muttath, Sureshkumar, M.D. NEWSOMET_MUTTATH_C_MDR000001-000081
Muttath, Sureshkumar, M.D. NewsomeT-SMMLMR- 00001-00010
Muttath, Sureshkumar, M.D. NewsomeT-SMMLMR-00011-00027
Myriad Genetics NewsomeT-MyrdGeneIncMR-00001-00018
Newsome, Tamara NEWSOMET_REC000001-000010
Steren, Albert NEWSOMET_PWHS_MDR000001-000003
Community Radiology Associates NEWSOMET_CRA_MDR000001-23
Maryland Oncology Hematology - Annapolis - NEWSOMET_MOHA_C_MDR000004-79
Maryland Oncology Hematology - Annapolis (NEWSOMET_MOHA_MDR000003-29)
Steren, Albert (NEWSOMET_PWHS_MDR000004-60)

Sureshkumar Muttath, MD - NEWSOMET_MUTTATH_MDR000081-106

Other Documents

Expert Report of John Godleski, M.D., dated June 24, 2021.

Report of William E. Longo, Analysis of Tamara Newsome's JBP containers, dated November 17, 2023.

Exhibit C

Daniel Clarke-Pearson, MD
Medical Legal Testimony in last 5 years

Date: January 7, 2019
Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Product Liability Litigation MDL No. 2738

March 27, 2020
Khan v. Karl Storz, Howard Jones, Noh Goodman, Valley Health System
SUPERIOR COURT OF NEW JERSEY
2 LAW DIVISION - ESSEX COUNTY

March 9, 2021
Case: Ruscitto v. Jones

Date: September 13, 2021 and September 14, 2021
Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Product Liability Litigation MDL No. 2738

Date: January 17, 2024 and March 8, 2024
Johnson & Johnson Talcum Powder Products Marketing, Sales Practices and Product Liability Litigation MDL No. 2738

Hourly Rate: $900/hour

EXHIBIT 42

WOMEN'S HEALTH SPECIALISTS OF MONTGOMERY COUNTY LLC • 12800 MIDDLEBROOK ROAD, GERMANTOWN, MD 20874-5204

NEWSOME, TAMARA (id #[redacted], dob: [redacted])

Clinical Document - Operative Note - 03/23/2015

PATIENT NAME: NEWSOME, TAMARA
MR#: 918132
DATE OF SERVICE: 03/23/2015
ACCT#: 56232875081
DOB: [redacted]
LOCATION: PACU
DICTATED BY: ALBERT J STEREN MD

I/P Operative Report

DATE OF SURGERY:
03/23/2015

SURGEON:
Albert Steren, M.D.

FIRST ASSISTANT:
Nadine Thompson, PA-C

FELLOW:
Tieneka Baker D.O.

PREOPERATIVE DIAGNOSES:
1. [redacted]

POSTOPERATIVE DIAGNOSIS:
[redacted]

PROCEDURE:
[redacted]

FINDINGS:
[redacted]

NOTE:
[redacted]

DESCRIPTION OF PROCEDURE:
[redacted]

WOMEN'S HEALTH SPECIALISTS OF MONTGOMERY COUNTY LLC • 12800 MIDDLEBROOK [redacted] GERMANTOWN, MD 20874-5204

NEWSOME, TAMARA (id [redacted], dob: [redacted])

[redacted]

R: 03/23/2015 13:43:54
T: 03/23/2015 14:23:53
J: 589795 AJS/IN
D: 693488

CC :

Lab Results

SURGICAL PATHOLOGY FINAL REPORT 04/14/2015 (#45973, Corrected, 03/23/2015 12:59pm)

Ordering Provider	ALBERT J. STEREN, MD	Performing Lab	TRINITY HEALTH 27870 CABOT DRIVE NOVI MI 48377
Specimen/Accession ID	7675777068	Specimen Source	
Specimen Coll. Date	03/23/2015 12:59	Result Status	Corrected
Specimen Rec. Date		Report Status	
Specimen Reported Date	04/14/2015 12:20		

Report	Result	Ref. Range	Units	⚠	Status	Lab
SURGICAL PATHOLOGY					Corrected	

[redacted]

EXHIBIT 43

PLAINTIFF PROFILE FORM

This Plaintiff Profile Form ("PPF") must be completed by the plaintiff or the representative of plaintiff's decedent. In completing this PPF, you are under oath and must provide information that is true and complete to the best of your knowledge, information and belief after reasonable inquiry. You must supplement your responses if you learn that they are incomplete or incorrect in any material respect.

In filling out this PPF, please use the following definitions: (1) "**health care provider**" means any hospital, clinic, medical center, physician's office, infirmary, medical or diagnostic laboratory, or other facility that provides medical, dietary, psychiatric, or psychological care or advice, and any pharmacy, weight loss center, x-ray department, laboratory, physical therapist or physical therapy department, rehabilitation specialist, physician, psychiatrist, osteopath, homeopath, chiropractor, psychologist, nutritionist, dietician, or other persons or entities involved in the evaluation, diagnosis, care, and/or treatment of the plaintiff or plaintiff's decedent; (2) "**document**" means any writing or record of every type that is in your possession, including but not limited to written documents, documents in electronic format, cassettes, videotapes, photographs, charts, computer discs or tapes, and x-rays, drawings, graphs, phone-records, non-identical copies, and other data compilations from which information can be obtained and translated, if necessary, by the respondent through electronic devices into reasonably usable form.

Information provided in this PPF will only be used for purposes related to this litigation and may be disclosed only as permitted by the protective order in this litigation. This PPF is completed pursuant to the Federal Rules of Civil Procedure governing discovery.

1. CASE INFORMATION

Name of Person Completing Form:	Pasqualina First	M.I.	Rausa Last
If you are completing this PPF in a representative capacity (e.g., on behalf of the estate of a deceased person), please complete the following:			
Your Name:	 First	M.I.	 Last
Your relationship to individual you represent:			

THE REST OF THIS PLAINTIFF PROFILE FORM REQUESTS INFORMATION ABOUT THE PERSON WHO USED JOHNSON'S BABY POWDER AND/OR SHOWER TO SHOWER AND WAS DIAGNOSED WITH OVARIAN CANCER

2. PERSONAL INFORMATION

Name:	Pasqualina First	M.I.	Rausa Last	
Maiden/Other Names Used:	Pasqualina Cefaloni			
Current or Last Known Address:	[redacted]	Ponte Vedra	FL	32081
Date of Birth: [redacted] [redacted] 1955		Gender:	Male: ☐	Female: ☑
Date of Death (If Applicable): ☑ N/A		Social Security Number: [redacted]		
Select Marriage Status: Married	Name of Spouse, if Married at time of filing Complaint: Joseph A. Rausa			

3. **TALCUM POWDER-RELATED CLAIM**

a. Have you been diagnosed with one of the following types of cancer? b. If yes, please provide the approximate date of initial diagnosis (if more than one, for each initial diagnosis). c. If you were diagnosed with ovarian cancer, fallopian tube or primary peritoneal cancer, please provide the type. d. If you were diagnosed with ovarian cancer, fallopian tube or primary peritoneal cancer, please provide the stage.

a. Type of Cancer	b. Date of Initial Diagnosis	c. Type of Ovarian, Fallopian tube, or Primary Peritoneal Cancer	d. Stage of Ovarian, Fallopian tube or Primary Peritoneal Cancer
Ovarian	Jun 13 2018	High-Grade Serous	Stage III

4. **MEDICAL HISTORY:**

[redacted]

c. Have you ever been diagnosed with any of the following?

Condition	Yes/No/Unknown	Name and Address of Diagnosing Provider	Approximate Date of Diagnosis (if applicable)
BRCA1 or BRCA2 mutation	[redacted]		
Endometriosis			
Adenomyosis			
Irregular vaginal bleeding			
Ovarian Cysts			
Polycystic ovaries and/or Polycystic Ovarian Syndrome (PCOS)			
Uterine fibroids			
Infertility			
Breast cancer			
Lynch Syndrome			

Condition	Yes/No/Unknown	Name and Address of Diagnosing Provider	Approximate Date of Diagnosis (if applicable)
Other cancer (please specify below):	[redacted]		
Obesity/overweight			
Pelvic Inflammatory Disease (PID)			
Colon Polyps			

6. *Other than* those injuries that you believe were caused by your use of body powder, do you currently suffer from any chronic illnesses or disabilities?

[redacted]

FAMILY MEDICAL HISTORY

7. Limiting this question to blood relatives, to the best of your knowledge, please indicate whether your *parents, siblings, children, grandparents, aunts, uncles, or first cousins* have ever suffered from or been treated for any type of cancer (including but not limited to ovarian cancer or breast cancer):

Relative's Name	Relation to you	Type of cancer	Date of cancer
[redacted]			

8. Limiting this question to blood relatives, to the best of your knowledge, please indicate whether your *parents, siblings, children, grandparents, aunts, uncles, or first cousins* have ever been diagnosed with any genetic mutations, including but not limited to BRCA1 or BRCA2 mutations?

[redacted]

HEALTH CARE PROVIDERS AND PHARMACIES

9. Limiting your answer to primary care, gynecology and oncology healthcare providers, identify each doctor or other health care provider who you have seen for medical care and treatment from the ten (10) years prior to your ovarian cancer diagnosis to the present. In particular, please use your best efforts to list all of the primary care providers during this period.

Doctor or Healthcare Provider's Name	Doctor or Healthcare Provider's Specialty	Address	Approximate Years of Visits
[redacted]			
			to
			to
			to

Doctor or Healthcare Provider's Name	Doctor or Healthcare Provider's Specialty	Address	Approximate Years of Visits
			to
			to
			to
			to
			to
			to
			to
			to
			to
			to
			to
			to
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			to
			to
			to

10. If any of your healthcare providers who you have seen in relation to treatment and care of **ovarian cancer or any other form of cancer** were not identified previously, please identify for each such provider:

Name and Specialty	Address	Approximate Years of Treatment	Reason for Treatment
[redacted]			
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	
		to	

11. Limiting your response to visits for issues related to cancer and to gynecologic issues other than pregnancy, identify each hospital, clinic, or health care facility where you were hospitalized (inpatient, out-patient, or emergency room visit) from the (10) years prior to your ovarian cancer diagnosis to the present:

Name	Address	Admission Date(s)	Reason for Admission Approx. Years of Visits
[redacted]			

Name	Address	Admission Date(s)	Reason for Admission Approx. Years of Visits

12. To the best of your recollection, identify each pharmacy that has regularly dispensed medication to you from the ten (10) years prior to your ovarian cancer diagnosis to the present:

Name of Pharmacy	Address of Pharmacy	Approx. Years You Used Pharmacy
[redacted]		
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to

Name of Pharmacy	Address of Pharmacy	Approx. Years You Used Pharmacy
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to
		to

13. Has any health care provider told you the cause(s) of your ovarian cancer?

[redacted]

Healthcare Provider's Name	Approximate Date of Conversation	Substance of Conversation

14. Have you had any communications with your health care providers, orally or in writing, about whether your condition is related to your use of Johnson's Baby Powder and/or Shower to Shower?

[redacted]

Healthcare Provider's Name	Approximate Date of Conversation

TALCUM POWDER PRODUCT USE

16. Have you ever used Johnson's Baby Powder? Choose Yes/No: Yes

If yes, identify:

a) Did you apply the product to your genital area? Choose Yes/No: Yes

b) Approximate year of first use: 1968

c) Approximate year of last use: 2018

d) Frequency of use during these dates: Once a day

17. Have you ever used Johnson & Johnson Shower to Shower? Choose Yes/No: Yes

If yes, identify:

a) Did you apply the product to your genital area? Choose Yes/No: Yes

b) Approximate year of first use: 1968

c) Approximate year of last use: 2018

d) Frequency of use during these dates: Once a day

18. Have you ever used any other cosmetic powder product(s) in your genital area?

Choose Yes/No: _____

If yes, identify:

a) Name of product(s): _____

b) Approximate year of first use: _____

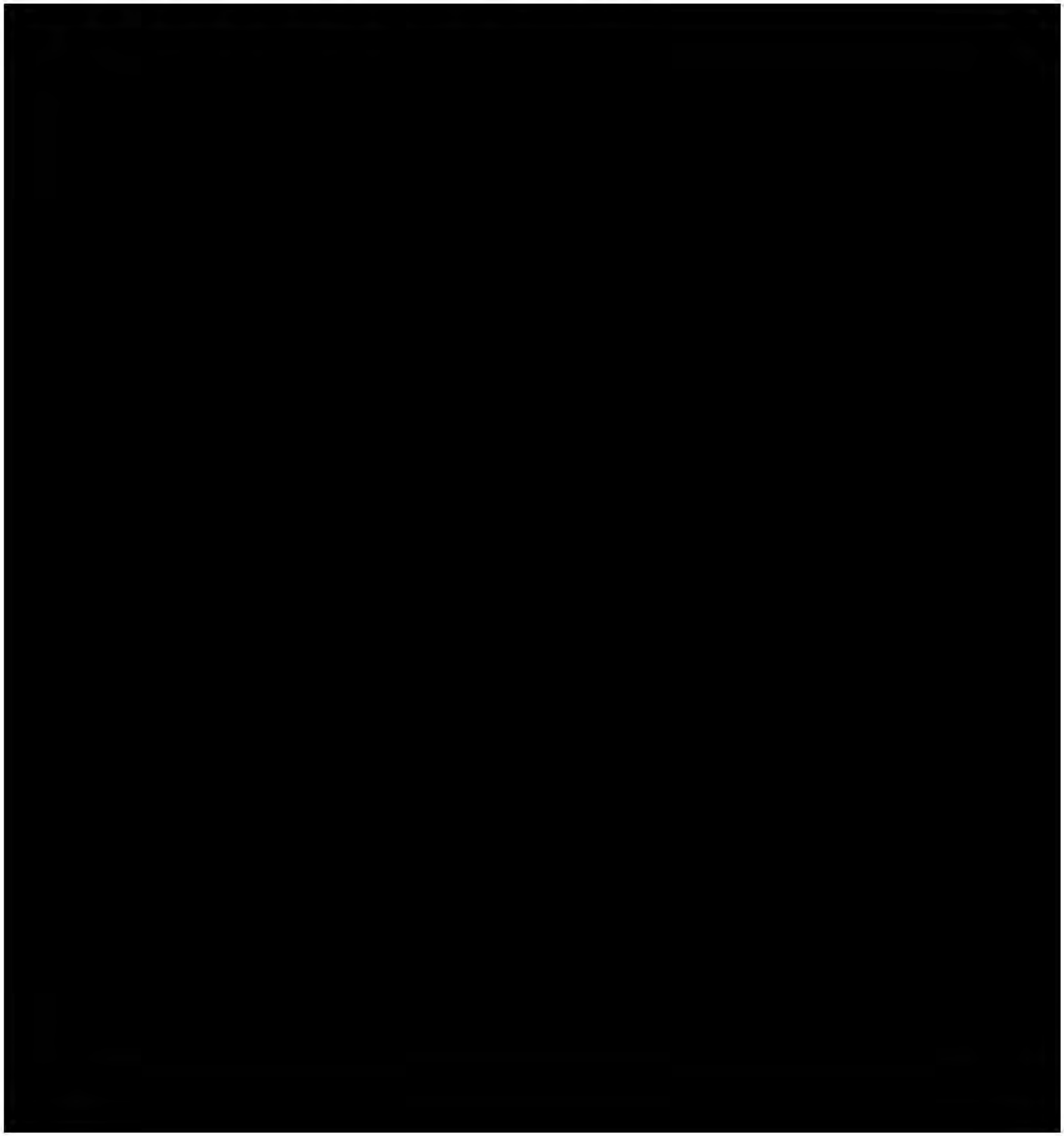
c) Approximate year of last use: _____

a) Name of product(s): _____

b) Approximate year of first use: _____

c) Approximate year of last use: _____

MEDICAL BACKGROUND OF BODY POWDER USER



24. **Employment History:**

Are you currently employed? Choose Yes/No: No
If yes, please identify your current employer and position:

25. **Education:**

Highest Educational Degree	Educational Institution
High School Diploma	Monsignor Scanlan High School

DOCUMENT DEMANDS

Documents in your possession, including writings on paper or in electronic form (if you have any of the following materials in your custody or possession, please indicate which documents you have and attach a copy of them to this Plaintiff Profile Form):

1. All documents relating to plaintiff's purchase(s) or acquisition(s) of Johnson's Baby Powder or Shower to Shower, including but not limited to, store receipts, credit card receipts, containers, labels, or other records of purchase or acquisition.

2. All medical records, reports, and/or documents from any hospital, physician, or other health care provider who treated plaintiff for ovarian cancer or any gynecologic disease, condition or symptom alleged in the Complaint and/or PPF.

3. If applicable, decedent-user's death certificate and copies of letters testamentary or letters of administration confirming standing of the named plaintiff.

4. A copy of all pathology reports related to plaintiff's/decedent's diagnosis or recurrence of ovarian cancer.

5. A copy of all reports reflecting any genetic testing undertaken on plaintiff/decedent.

DECLARATION

I declare under penalty of perjury that all of the information provided in connection with this Short Form Plaintiff Profile Form is true and correct to the best of my knowledge, information, and belief formed after due diligence and reasonable inquiry. I acknowledge that I have an obligation to supplement the above responses if I become aware of additional responsive information, or if I learn that they are in some material respects incomplete or incorrect.

Date: _____

_____

Signature of Plaintiff

_____

Print Name of Signing Plaintiff

EXHIBIT 44

DukeHealth

Rausa, Pasqualina
MRN: [redacted], DOB: [redacted], Sex: F
Encounter Date 2/8/2018

Vitals (continued) Most recent update: 2/8/2018 1:48 PM

BP	Pulse	Ht	Wt	BMI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Pain Information (Last Filed)

Score	Location	Comments	Edu?
[redacted]	[redacted]	[redacted]	[redacted]

PROVIDER PROGRESS NOTES

Progress Notes by Highley, Louise Langdon, MD at 2/8/2018 1:30 PM

Author: Highley, Louise Langdon, MD | Service: — | Author Type: Physician
Encounter Date: 2/8/2018 | Filed: 2/8/2018 3:13 PM | Status: Signed
Editor: Highley, Louise Langdon, MD (Physician)

Chief Complaint: [redacted]

History of Present Illness: [redacted]

Past Gynecological History/ Health Maintenance: [redacted]

Obstetrical History:

OB History

Gravida	Para	Term	Preterm	AB	Living
[redacted]					

Medical History: [redacted]

Surgical History:

Past Surgical History:

Procedure	Laterality	Date
• [redacted]		

Social History: [redacted]

Social History

- Marital status: Married

EXHIBIT 45

ORIGINAL ARTICLE

Douching, Talc Use, and Risk of Ovarian Cancer

Nicole L. Gonzalez,[a] *Katie M. O'Brien,*[a] *Aimee A. D'Aloisio,*[b] *Dale P. Sandler,*[c] *and Clarice R. Weinberg*[a]

Background: Douching was recently reported to be associated with elevated levels of urinary metabolites of endocrine disrupting phthalates, but there is no literature on douching in relation to ovarian cancer. Numerous case–control studies of genital talc use have reported an increased risk of ovarian cancer, but prospective cohort studies have not uniformly confirmed this association. Behavioral correlation between talc use and douching could produce confounding.

Methods: The Sister Study (2003–2009) enrolled and followed 50,884 women in the US and Puerto Rico who had a sister diagnosed with breast cancer. At baseline, participants were asked about douching and talc use during the previous 12 months. During follow-up (median of 6.6 years), 154 participants reported a diagnosis of ovarian cancer. We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for ovarian cancer risk using the Cox proportional hazards model.

Results: There was little association between baseline perineal talc use and subsequent ovarian cancer (HR: 0.73, CI: 0.44, 1.2). Douching was more common among talc users (odds ratio: 2.1, CI: 2.0, 2.3), and douching at baseline was associated with increased subsequent risk of ovarian cancer (HR: 1.8, CI: 1.2, 2.8).

Conclusions: Douching but not talc use was associated with increased risk of ovarian cancer in the Sister Study.

(*Epidemiology* 2016;27: 797–802)

Cancer of the ovary is the most lethal gynecological cancer in women, and its etiologies remain poorly understood. In 2015, there were an estimated 21,290 new cases and 14,180 ovarian cancer deaths among women in the United States.[1] Family history of ovarian or breast cancer is a major risk factor. Nulliparity is also associated with increased risk of ovarian cancer, whereas tubal ligation and oral contraceptive use are reportedly associated with reduced risk.[2]

Genital talc use and douching could plausibly introduce particles and toxicants into the upper reproductive tract and increase the risk of cancers and infections. Talc particles have been found embedded in cervical and ovarian tumors.[3] Fragranced douching products can contain phthalates, which disrupt endocrine pathways and could influence ovarian cancer risk through hormone disruption.[4] A recent analysis of data from the National Health and Nutrition Examination Survey found an association between douching and urinary concentrations of phthalates.[5] Douching has also been associated with adverse health effects and reproductive problems, such as pelvic inflammatory disease and ectopic pregnancy,[6] as well as decreased fertility.[7]

To the best of our knowledge, no existing studies have investigated the association between douching and ovarian cancer, but talc use was associated with ovarian cancer in many case–control studies.[8–13] A meta-analysis of 14 population-based, case–control studies[14] and a large, pooled case–control analysis[15] both reported positive associations between genital talc use (ever vs. never) and ovarian cancer. The only prospective studies to examine talc and ovarian cancer[16,17] found no strong associations overall, but one observed increased risk for invasive serous ovarian cancer, specifically.[17] In this study, we investigate the association between ovarian cancer and both douching and talc use, using prospective data from the Sister Study cohort.

METHODS

The Sister Study, launched in 2003, enrolled 50,884 women across the United States and Puerto Rico. Enrollees were aged 35 to 74 years and had never had breast cancer but each had a full or half-sister who had been diagnosed with breast cancer. More than one sister per family could participate.

After excluding participants who had bilateral oophorectomies (N = 9,023) or ovarian cancer (N = 167) before enrollment or who had no follow-up information (N = 40), we included 41,654 participants in this analysis. As of July 2014 (median follow-up 6.5 years), 154 incident ovarian cancer cases had occurred. We included tumors of the ovary (N = 135), fallopian tubes (N = 7), peritoneum (N = 4), or of uncertain origin but likely from one of the three aforementioned

Submitted 18 April 2016; accepted 15 June 2016.

From the [a]Biostatistics and Computational Biology Branch, National Institute of Environmental Health Sciences, Research triangle Park, NC; [b]Social & Scientific Systems, Inc., Durham, NC; and [c]Epidemiology Branch, National Institute of Environmental Health Sciences, Research triangle Park, NC.

Supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (Project Z01-ES044005 to DPS).

Dale P. Sandler and Clarice R. Weinberg are joint senior authors.

The authors report no conflicts of interest.

SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

Correspondence: Clarice R. Weinberg, 111 TW Alexander Dr, Research triangle Park, NC 27709. E-mail: weinber2@niehs.nih.gov.

ISSN: 1044-3983/16/2706-0797
DOI: 10.1097/EDE.0000000000000528

primary sites (N = 8). The Institutional Review Boards of the National Institute of Environmental Health Sciences and the Copernicus Group approved this study and all participants provided written consent.

Participants completed computer-assisted telephone interviews, which included questions about reproductive history (including any oophorectomies), health conditions, and lifestyle factors. Participants also completed a self-administered questionnaire about personal care products used in the 12 months before enrollment, which included questions about frequency of douching and about genital talc use in the form of powder or spray applied to a sanitary napkin, underwear, diaphragm, cervical cap, or vaginal area. Response categories were: did not use, used less than once a month, used 1–3 times per month, 1–5 times per week, or more than 5 times per week. Because most members of the cohort reported not douching and not using talc, we used dichotomous use/nonuse variables for analysis.

Updated information on oophorectomies was collected in follow-up questionnaires administered every 2–3 years. We ascertained information on any new cancers via an annual health update and the follow-up questionnaires and were able to confirm 96 of the ovarian cancer cases using medical records (N = 87) or death certificate/National Death Index data (N = 9). For the remaining 58 cases, we relied on information provided by the participant herself (N = 52) or her next of kin (N = 6). Among women with available medical records who self-reported ovarian cancer, 90% were confirmed.

There were five eligible cases with an unknown exact age at diagnosis. For them, we imputed an age midway between their last ovarian cancer-free follow-up interview and their age at the time we were notified of the diagnosis (or death). Although we did not genotype women directly for *BRCA1* or *BRCA2* mutations, we asked each woman in her baseline interview whether she had ever been tested and, if so, what the result of those tests were. For the purposes of this analysis, a woman was treated as *BRCA1/2* mutation positive if (1) she had a positive test or (2) she had a sister with a known positive test and she had no known negative test.

Statistical Analyses

We computed adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of talc use and douching with ovarian cancer risk using Cox proportional hazards models, with age as the primary time scale. Follow-up lasted from age at baseline until age at diagnosis of ovarian cancer. Follow-up time was censored at their age of bilateral oophorectomy after baseline, death, or last contact. Because some participants had sisters who also enrolled in the cohort, we used generalized estimating equation methods to calculate robust variances to account for family clustering. We evaluated proportionality assumptions of the Cox model by assessing the improvement in goodness-of-fit provided by including an age-by-factor interaction term.

In addition to the main effect, we evaluated the joint effect of both douching and using talc. We classified participants into four categories: neither exposure, talc use exclusively, douching exclusively, or both exposures. We also carried out a number of stratified analyses. We stratified by reproductive factors, such as menopausal status, parity, hysterectomy, and tubal ligation to explore possible effect modification.[10,13] We tested for differences across strata using the *P* value for an exposure-by-modifier interaction term.

We selected potential confounders or effect modifiers of the association between ovarian cancer and the exposures of interest in this analysis a priori based on assumed causal relationships among the covariates,[18] and included patency (yes/no blockage of reproductive tract by tubal ligation or hysterectomy), menopausal status (pre- or postmenopausal), duration of oral contraceptive use (none, <2 years, 2-<10 years, 10 or more years), parity (yes/no), race (non-Hispanic white, non-Hispanic black, Hispanic or other), and body mass index (<25, 25–29.9, or >30 kg/m^2), all of which were fixed at baseline levels.

We conducted six sensitivity analyses. In the first, we restricted to the 96 cases confirmed by medical record or death certificate/National Death Index data. For our second sensitivity analysis, we looked for evidence of etiologic heterogeneity by further restricting this pool to medically confirmed cases with serous ovarian cancer (N = 49). For our third sensitivity analysis, we included all 154 eligible ovarian cancer cases as well as five additional cases that had unknown ages at diagnosis and prebaseline oophorectomies (N = 159 cases total). We did this to examine the influence of our assumptions about the relative timing of their oophorectomies versus their ovarian cancer diagnoses. We further examined the influence of imputing age at diagnosis in our fourth sensitivity analysis by excluding the five cases with imputed diagnosis ages but intact ovaries (N = 149 cases total). For our fifth sensitivity analysis, we excluded participants from families known to carry *BRCA* mutations (N = 347 exclusions, including 10 cases) since the lifetime risk of ovarian cancer for individuals with a *BRCA1/2* mutation is substantially higher[19] and the etiology may be different. Finally, we conducted analyses excluding the first year of follow-up, to minimize the possibility that symptoms of undiagnosed ovarian cancer were leading participants to use douche or talc. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC) and using the Sister Study data release version 4.1.

RESULTS

Table 1 summarizes characteristics of cases and noncases at baseline. Most participants were non-Hispanic white (84%), and most were postmenopausal (56%). Women who later became cases were somewhat older (mean 57.8 vs. 54.8), more often white, and more often nulliparous. Cases were also more likely to have a first-degree family history of ovarian cancer and more than one first-degree relative with

TABLE 1. Baseline Characteristics of the Sister Study Cohort (2003–2009)[a]

	Noncases (N = 41,500)	Ovarian Cancer Cases (N = 154)
Race; N (%)		
Non-Hispanic White	34,745 (84)	138 (90)
Non-Hispanic Black	3,598 (9)	9 (6)
Hispanic	2,076 (5)	5 (3)
Other	1,068 (2)	2 (1)
Education; N (%)		
High school or less	6,001 (14)	24 (15)
Some college	13,556 (33)	49 (32)
Bachelor's degree	11,579 (28)	46 (30)
Graduate degree	10,354 (25)	35 (23)
BMI; N (%)		
<25.0 kg/m^2	16,610 (40)	51 (33)
25–29.9 kg/m^2	13,012 (31)	51 (33)
≥30 kg/m^2	11,866 (29)	52 (34)
Menopausal status; N (%)		
Premenopausal	15,238 (37)	40 (26)
Hysterectomy with ovaries retained	2,996 (7)	8 (5)
Postmenopausal	23,239 (56)	106 (69)
Hysterectomy; N (%)		
No	34,481 (83)	120 (78)
Yes	6,995 (17)	34 (22)
Tubal ligation; N (%)		
No	29,511 (71)	115 (75)
Yes	11,973 (29)	39 (25)
Oral contraception		
Duration of Use; N (%)		
None	6,452 (16)	25 (16)
<2 years	6,382 (15)	37 (24)
2–10 years	17,769 (43)	67 (44)
10 years or more	10,865 (26)	25 (16)
Parity; N (%)		
No live births	7,657 (18)	37 (24)
1 or more live births	33,816 (82)	116 (76)
First-degree family history of ovarian cancer; N (%)		
No	40,149 (97)	138 (90)
≥1 first-degree relative	1,322 (3)	16 (10)
Breast cancer; N (%)		
1 affected sister	31,291 (75)	109 (71)
>1 sister or sister + mom	10,207 (25)	45 (29)
BRCA1/2 mutation status; N (%)		
No known mutation	41,163 (99)	144 (94)
Known mutation	337 (1)	10 (6)

Missing values: race (13 noncases), education (10 noncases), BMI (12 noncases), menopausal status (27 noncases), tubal ligation (16 noncases), hysterectomy (24 noncases), oral contraception use (32 noncases), parity (1 case, 27 noncases), ovarian cancer family history (29 noncases), and breast cancer family history (2 noncases).

[a]Excludes women who were diagnosed with ovarian cancer before completion of the baseline interview (N = 167), women who had a bilateral oophorectomy before the baseline interview (N = 9,023), and women lost to follow-up (N = 40).

BMI indicates body mass index.

breast cancer. They were also more likely to carry a deleterious mutation in *BRCA1* or *BRCA2*. While ever/never use of oral contraceptive was similar across cases and noncases, the distribution of duration of use differed. More noncases (26%) than cases (16%) had used oral contraceptives for more than 10 years. Compared with women who neither douched nor used talc, women who douched were more likely to be non-Hispanic black (23% vs. 6%) and to have less than a college degree (62% vs. 44%) and women who used talc were more likely to have a body mass index over 30 kg/m^2 (41% vs. 25%; eTable; http://links.lww.com/EDE/B74).

Douching in the 12 months before study enrollment was reported by 13% of noncases and 20% of cases (Table 2). Talc use in the 12 months before study enrollment was reported by 14% of noncases and 12% of cases. Only seven cases (5%) reported both douching and talc use.

Ever douching during the 12 months before study entry was associated with increased ovarian cancer risk (adjusted HR: 1.8, 95% CI: 1.2, 2.8; Table 2). By contrast, talc use during the 12 months before study entry was associated with reduced risk after the same confounder adjustments (HR: 0.73, CI: 0.44, 1.2) and there was a negligible change in the estimated effect with additional adjustment for douching (HR: 0.70, CI: 0.42, 1.1). We observed no proportional hazards assumption violations for any of the examined models.

Douching with no talc use was also associated with increased risk of ovarian cancer compared with use of neither talc nor douching (adjusted HR: 1.9, CI: 1.2, 2.9), which is similar to the overall effect estimate of douching. There was an inverse association between exclusive talc use and ovarian cancer, and a positive association for douching and talc use combined (HR: 1.8, CI: 0.81, 3.9). There was no evidence for interaction on a multiplicative ($P = 0.39$) or additive ($P = 0.72$) scale.

To explore effect modification, we performed analyses stratified by a number of reproductive factors including tubal ligation status, hysterectomy status, menopause status, and parity (Figure). We also stratified by patency to see if blockage of access to the ovaries by either tubal ligation or hysterectomy might modify the association between ovarian cancer and douching or talc use. For all stratifications, there were no modifications of effect estimates for either douching or talc use (all heterogeneity P values >0.05).

HRs for talc use differed little in the first five sensitivity analyses, showing a HR change no greater than 0.04. By contrast, exclusion of ovarian cancers without medical record or death certificate confirmation (by censoring their follow-up at the reported diagnosis age) attenuated the association between douching and ovarian cancer (HR: 1.1, CI: 0.62, 2.1). Likewise, restriction to medically confirmed serous ovarian cancer also attenuated effect estimates (HR: 1.4, CI: 0.64, 3.2). However, ovarian cancer cases who had reported that they douched were substantially less likely to have a medical record available (40%) than ovarian cases who did not douche (69%),

suggesting that medical records were informatively missing, biasing results based on the restricted analysis. There was very little change in douching effect estimates when excluding the five cases with uncertain diagnosis dates or including the five women reporting oophorectomies before the diagnosis of ovarian cancer. Exclusion of known positive *BRCA1/2* families slightly strengthened the association between douching and ovarian cancer (HR: 1.9, CI: 1.3, 2.9). In our sixth sensitivity analysis, exclusion of the first year of follow-up time resulted in negligible changes in the HRs for douching and talc use (HR: 1.8, CI: 1.2, 2.8 and HR: 0.86, CI: 0.52, 1.4, respectively).

DISCUSSION

In this large prospective cohort, which gave rise to 154 incident cases of ovarian cancer, there was a positive association between douching and incident ovarian cancer. Talc use was associated with a slight reduction of ovarian cancer risk. Our study of ovarian cancer grouped together all cancers designated as ovarian (88%), fallopian (5%), peritoneal (3%), or those designated as uncertain but ovarian, fallopian, or peritoneal (5%). With recent literature suggesting that most cancers classified as ovarian likely originated in the fallopian tubes,[20] we felt that this grouping was appropriate.

Interest in talc as a carcinogen arose because of its chemical similarity to asbestos, which has been previously linked to ovarian cancer.[21] One challenge with studying talc is that the chemical formulation of talc has changed over time,[9] and not all powders contain the mineral talc (e.g., cornstarch-based products). Previous case–control studies have noted evidence for a positive association,[8–13] with some evidence that the effect is strongest in premenopausal women.[13] Given these results, the biological plausibility, the rarity of the exposure, and imprecision of estimates, we cannot exclude a small increase in risk associated with talc use, despite our inverse findings. Then again, with the exception of the finding that talc use was positively associated with serous ovarian cancer in the Nurses' Health Study,[17] the prospective studies have not provided evidence supporting an association between talc use and ovarian cancer overall[17] or between talc use and ovarian cancer overall among postmenopausal women.[16]

The numbers for the Sister Study as a whole given in Table 2 reveal an odds ratio of 2.1 (CI: 2.0, 2.3) for douching in relation to talc use. Thus, the two practices are correlated. If douching is a risk factor for ovarian cancer, some of the earlier reports on talc could have been subject to confounding bias. However, the one case–control study that did include douching as a covariate still observed a positive association between talc use and ovarian cancer risk.[8] Another factor that may contribute to our null findings is that we categorized the exposure based on the 12 months before enrollment as a dichotomous ever/never factor rather than a quantitative measure of total applications, as has been done in previous studies.

Because Sister Study participants all have a first-degree family history of breast cancer, they are more likely than the general population to develop ovarian cancer (estimated observed/expected number of cases = 1.6 based on SEER rates). We also note that, by design, we excluded women with a previous history of breast cancer, thereby discounting some individuals who were at increased risk for ovarian cancer. While these selective factors may limit generalizability, there is no clear mechanism by which they would bias the estimated effect of talc use or douching on ovarian cancer.

Our review of the literature suggests that our study is the first to examine the association between douching and ovarian cancer. This association could reflect uncontrolled confounding by behavioral factors we have not captured well. For example, women may be more likely to douche if they are prone to infections or other reproductive health problems that could themselves be related to ovarian cancer.

If the association is causal, it could be related to the recently reported positive association between douching

TABLE 2. Exposure Prevalence and Hazard Ratios for Their Associations with Ovarian Cancer in the Sister Study

	Noncases (N = 41,500)	Ovarian Cases (N = 154)	Fully Adjusted Hazard Ratio[a]
Douching past 12 months			
No	34,653 (87)	121 (80)	1.00
Yes	5,364 (13)	30 (20)	1.8 (1.2, 2.8)
Talc use past 12 months			
No	33,770 (86)	130 (88)	1.00
Yes	5,718 (14)	17 (12)	0.73 (0.44, 1.2)
Douched and used talcum powder past 12 months			
Neither	29,596 (76)	106 (72)	1.00
Talc use/no douching	4,399 (11)	10 (7)	0.60 (0.31, 1.1)
Douching/no talc use	3,936 (10)	23 (16)	1.9 (1.2, 2.9)
Both	1,237 (3)	7 (5)	1.8 (0.81, 3.9)

Missing values: douching (3 cases, 1,483 noncases), talc use (7 cases, 2,012 noncases).
[a]Adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency.

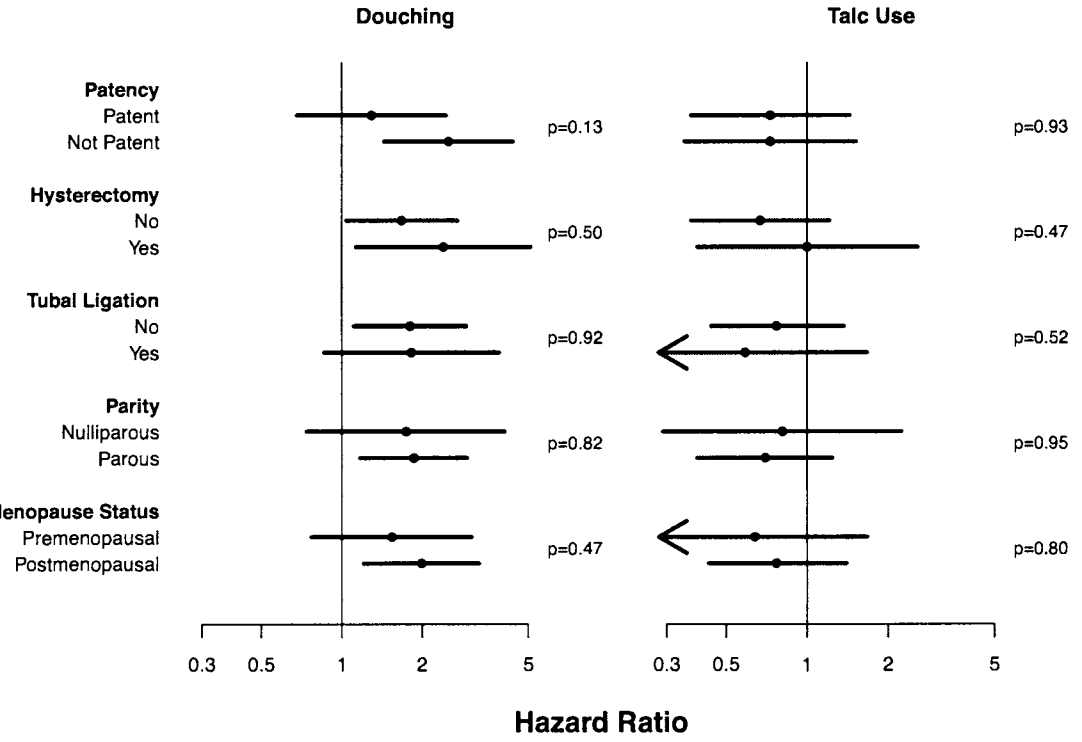


FIGURE. Effect estimates of douching and talc use in the Sister Study when stratified by multiple reproductive factor, adjusted for race, body mass index, parity, duration of oral contraceptive use, baseline menopause status, and patency. The reported heterogeneity *P* values are for tests of an exposure-by-modifier interaction term.

and higher urinary levels of phthalate metabolites observed in National Health and Nutrition Examination Survey participants.[5] Phthalates are endocrine-disrupting chemicals and may be harmful to the fallopian tubes or the ovaries.[22] In an animal study, exposure to di-(2-ethylhexyl) phthalate at 500 and 2,000 mg/kg demonstrated ovarian toxicity through decreased progesterone and increased apoptosis in granulosa cells.[23] Furthermore, ovarian cancer cell lines have been found to increase cell proliferation and to up-regulate cell-cycle regulatory genes following treatment with di-*n*-butyl phthalate.[24] We did not collect detailed information about specific products used in douching, so we are unable to estimate exposure to individual phthalates.

Douching could also force tissue, menstrual fluids, or foreign materials up the reproductive tract, resulting in inflammation (e.g., pelvic inflammatory disease[6]) or infection of the fallopian tubes or ovaries themselves. This inflammation and infection could also contribute to ovarian cancer risk, as supported by the observed positive association between pelvic inflammatory disease and ovarian cancer.[25]

If the association is causal and related to the transfer of xenobiotics into the upper reproductive tract, we would expect to see a stronger association in women with both a uterus and patent fallopian tubes. However, the evidence in our data appeared to be driven by the subcohort of women with hysterectomy and/or tubal ligation (Figure).

Because our study was prospective in nature, it is robust to potential differential reporting bias as exposures are recorded before development of cancer. Another important strength of the study was that we controlled for many potentially confounding factors.

An important limitation of our study is that we collected douching and talc information on individuals for the year before study entry and have not accounted for the latency of ovarian cancer, which is likely to be long.[26] If latency is 15 to 20 years, douching habits at baseline do not accurately reflect the period of risk, although women who douched at baseline are likely to have been douching for a substantial amount of time before that as well. Also, given that there have been health advisories against douching because of its other potential risks, participants who douched in the past may have stopped douching and would be misclassified. Thus, the relative risk for douching in relation to ovarian cancer could be underestimated. Future studies that ascertain a complete history of douching are warranted.

Although the baseline questionnaire did ask women about their use of douche and talc between the ages 10 and 13, very few women responded yes to douching (2%), and we were unable to make use of those data. By contrast, talc use during ages 10–13 had a prevalence of 18% in the cohort, but there was no detectable effect of prepubertal talc use on risk (HR: 1.1, CI: 0.74, 1.7).

Exposure information was very complete, with only 831 participants (2%) missing the personal care products questionnaire entirely, and an additional 655 and 1,188 missing data for the questions about douching or talc use, respectively. However, for approximately 37% of cases, we have not yet received medical records to confirm the diagnosis. We found that medical record retrieval was differential by exposure, with a lower proportion with medical records among women who douched than among women who did not. This informative missingness mathematically contributed to the substantial attenuation in the HR estimate for the association between vaginal douching and ovarian cancer when we restricted to cases with medical record confirmation. Medical record retrieval for ovarian cancer began only recently, and women with cancers diagnosed early in follow-up are more likely to be missing medical record information. Some of the unconfirmed diagnoses may be confirmed later via medical records or the national death index.

In this large, prospective study, we did not observe an association between recent talc use and ovarian cancer risk, but did find a strong positive association between douching and ovarian cancer risk.

ACKNOWLEDGMENTS

The authors thank Drs. Kristen Upson and Annah Wyss for comments on an early draft of this article.

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EXHIBIT 46

Environment International 183 (2024) 108298

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Full length article

Use of personal care product mixtures and incident hormone-sensitive cancers in the Sister Study: A U.S.-wide prospective cohort

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ARTICLE INFO

Handling Editor: Zorana Andersen

ABSTRACT

Background: Personal care products (PCPs), a source of endocrine-disrupting chemical exposure, may be associated with the risk of hormone-sensitive cancers. Few studies have investigated associations for PCP use with the incidence of hormone-sensitive cancers or considered the joint effect of multiple correlated PCPs. We examined associations between frequently used, or "everyday", PCPs and incident cancers of the breast, ovary, and uterus with a fucus on the joint effect of multiple product exposure.

Methods: Sister Study participants (n=49 899) self-reported frequency of use in the year before enrollment (2003–2009) for 41 PCPs. Using five-level frequency categories based on questionnaire options, hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated for the associations between multiple PCP use and incident breast, ovarian, and uterine cancer using quantile-based g-computation with Cox proportional hazards regression as the underlying model. Multiple PCP use was examined using groupings (beauty, hygiene, and skincare products) determined by both *a priori* knowledge and Spearman correlation coefficients for co-occurring product use. Associations between individual PCPs and the three cancers were also examined using Cox proportional hazards models coupling with Benjamini-Hochberg procedure for multiple comparisons.

Results: Over an average of 11.6 years, 4 226 breast, 277 ovarian, and 403 uterine cancer cases were identified. Positive associations were observed between the hygiene mixture and ovarian cancer (HR=1.35, 95%CI=1.00, 1.83) and the beauty mixture with postmenopausal breast cancer (HR=1.08, 95%CI=1.01, 1.16). Additionally, we observed an inverse association between the skincare mixture and breast cancer (HR=0.91, 95%CI=0.83, 0.99). No significant associations were observed for individual products after corrected for multiple comparison.

Conclusions: Findings from this multi-product, joint-effect approach contribute to the growing body of evidence for associations between PCPs and breast cancer and provides novel information on ovarian and uterine cancer.

1. Introduction

Breast, ovarian, and uterine cancer are considered hormone-driven cancers, with estrogen in particular thought to play a role in tumor development and growth. These cancers continue to be major health threats for women with an incidence slightly increasing worldwide (Yi et al., 2021). In 2022, cancers of the breast, ovary, and uterus were estimated to contribute to over 370 000 incident cases (>19% of all new cancer cases) and 68 610 deaths (>11% of all cancer deaths) in the U.S (Siegel et al., 2022).

Established risk factors for hormone-sensitive cancers, including obesity (Stephenson & Rose, 2003), early menarche (Collaborative Group on Hormonal Factors in Breast Cancer, 2012), parity (Lambe et al., 1996), and use of hormonal contraceptives (Mørch et al., 2017) or hormone replacement therapy (Narod, 2011), provide evidence for endocrine disruption and/or hormonal imbalance as key biologic pathways. There has been a growing interest in the role of endocrine-disrupting chemicals (EDCs) in hormone-sensitive cancer etiology given the shared secular trends for EDC production, precocious puberty, and breast cancer incidence (Bergman et al., 2013; Calaf et al., 2020;

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https://doi.org/10.1016/j.envint.2023.108298
Received 30 March 2023; Received in revised form 28 July 2023; Accepted 30 October 2023
Available online 2 November 2023

Lucaccioni et al., 2020). Some previous epidemiologic studies have investigated the associations between EDCs and hormone-sensitive cancers (Ahern et al., 2019; Liu et al., 2021; López-Carrillo et al., 2010; Parada et al., 2019; Reeves et al., 2019; Sarink et al., 2021; Wu et al., 2021). However, conclusions from these studies were inconsistent and limited, likely due to the use of transient exposure biomarkers to estimate relevant exposure levels to assess long-term risk of carcinogenesis (Zuccarello et al., 2018). Experimental studies have demonstrated the ability of different EDCs such as bisphenol A (Shi et al., 2017; Wang et al., 2016), triclosan (Farasani & Darbre, 2021), parabens (Charles & Darbre, 2013), and phthalates (Moral et al., 2011), to affect hormone-sensitive tumor development and progression, sometimes even at low-dose exposures.

PCPs have been important sources of chronic exposure to short-lived EDCs such as bisphenols, parabens, phthalates, triclosan, and fragrances (Branch et al., 2015; Braun et al., 2014; Dodson et al., 2012; Helm et al., 2018; Myers et al., 2015; Peinado et al., 2021; Sakhi et al., 2017). Although women are the primary consumers of PCPs and have been disproportionally burdened by EDC exposures (Biesterbos et al., 2013; Silva et al., 2004), few epidemiologic studies have investigated the contribution of PCP use to the risk of women's hormone-sensitive cancers. Existing research has largely focused on only certain products such as hair dyes, hair straighteners/relaxers, deodorant, genital talc, and douching products (Allam, 2016; Brinton et al., 2018; Chang et al., 2022; Eberle et al., 2020; Gonzalez et al., 2016; Goodman et al., 2020; Mousavi & Vaghar, 2021; O'Brien et al., 2019, 2021; Penninkilampi & Eslick, 2018; Rylander et al., 2019; Stiel et al., 2016; Taylor et al., 2018; Wentzensen & O'Brien, 2021; White et al., 2021), without considering a comprehensive list of more frequently used ("everyday") PCPs. Furthermore, due to the challenges of data collection on a wide range of PCPs and statistical methods for mixture analyses, previous studies predominately assessed the effect of individual products separately. Taking a single-product approach is limiting because it fails to account for potential confounding by concurrently used products and does not reflect the risk associated with multiple products simultaneously in real-life settings (Braun et al., 2014).

In this study, we aimed to examine the associations between the use of everyday PCPs and cancers of the breast, ovary, and uterus with a focus on joint effect of multiple product use in a large prospective cohort in the U.S. We also explored whether these relationships varied by race and ethnicity, and body mass index (BMI). Racial and ethnic differences in PCP use were observed previously (Collins et al., 2021; Dodson et al., 2021; Gaston et al., 2020; Preston et al., 2021; Wu et al., 2010), andthe products marketed toward or used often by women of color may contain more harmful and hormonally-active chemicals (Helm et al., 2018), which may contribute to a differential impact of PCP use on cancer development by race and ethnicity. We also hypothesized that the effect of PCP use may differ by BMI, as exogenous estrogens such as hormone replacement therapy have a reduced impact on breast and endometrial cancer in obese than lean women ("Endometrial Cancer and Hormone-Replacement Therapy in the Million Women Study," 2005; Hou et al., 2013).

2. Methods

2.1. Study design and population

The Sister Study is a prospective cohort that enrolled 50 884 women who lived in the United States, including Puerto Rico, from 2003 to 2009 (Sandler et al., 2017). Participants were eligible if they were between 35 and 74 years old at enrollment and had at least one sister diagnosed with breast cancer, but themselves were breast cancer-free. At baseline, participants completed a computer-assisted telephone interview and self-administered written questionnaires to assess demographics characteristics, lifestyle factors, and reproductive history. Weight and height were measured by trained examiners during a home visit at baseline. Participants are contacted annually for health updates regarding new cancer diagnoses and other health-related changes. More detailed follow-up assessments are collected every three years. Response rates have been above 80% throughout follow-up. Data for the current analysis included person-time through October 2020 (Data Release 10.1). Written informed consent was obtained from all participants, and the Sister Study is overseen by the institutional review boards of the National Institutes of Health.

Among 49 889 women who responded to at least one PCP question, we excluded women who withdrew from the study, had a pre-baseline diagnosis, an uncertain diagnosis, or an unclear timing of diagnosis (relative to enrollment) for the hormone-sensitive cancer of interest, or who did not contribute any follow-up time. For ovarian and uterine cancer analysis, we further excluded women who had a pre-baseline bilateral oophorectomy or hysterectomy, respectively. Thus, the numbers of eligible participants varied by analyses, with 49 578, 40 610, and 33 976 participants included in the breast, ovarian, and uterine cancer analyses, respectively.

2.2. Assessment for personal care product use

Participants completed a questionnaire at baseline about their use of PCPs in the previous 12 months. The questions collected information on the frequency of use of 41 PCPs, including 12 beauty products (blush/rouge, eyeliner, eye shadow, foundation, lipstick, mascara, perfume/cologne, makeup remover, artificial nails/fill-ins, cuticle cream, nail polish, and nail polish remover), seven everyday hair products (conditioner, hair food, hair spray, hair styling gel/mousse, Minoxidil/Rogaine, pomade/hair grease, shampoo), eight hygiene products (bath/shower gel, deodorant/antiperspirant, douche, mouthwash/rinse, shaving cream, talc [under arm], talc [genital], talc [other areas]), and 14 skincare products (anti-aging or wrinkle product, age spot lightener, baby oil/mineral-based oil, blemish/acne product, body lotion/cream, cleansing cream, face cream/moisturizer, facial mask, foot cream/moisturizer, hand lotion/cream, lip moisturizer, petroleum jelly, skin lightener, self-tanner) with the options of "did not use", "less than once a month", 1–3 times per month", "1–5 times per week", and "more than 5 times per week." We classified those options from low to high frequency of use as level one to five. Seven less frequently used hair products including permanent, semi-permanent, and temporary dyes, bleach, highlights, straighteners/relaxers or pressing products, and hair permanents/body waves were not considered, as use of these products is more episodic and thus would not regularly co-occur with the everyday PCPs.

2.3. Incident hormone-sensitive cancers

Participants who reported a diagnosis of breast, ovarian (including fallopian tube and peritoneal cancers), and/or uterine cancer were defined as cases. We further asked the women who reported a hormone-sensitive cancer diagnosis for permission to retrieve their medical records. About 89%, 78%, and 78% of the cases were confirmed with either medical records or death certificates indicating the primary or underlying cause of death as breast, ovarian, and uterine cancer, respectively. The positive predictive values of self-reported cases in relation to medically confirmed cases are high, with 99% for breast, 80% for ovarian, and 81% for uterine cancer (The Sister Study: Breast Cancer Validation, 2022); thus, all self-reported cases were included in the main analyses.

We also abstracted information on cancer subtypes such as estrogen receptor (ER) status of breast cancer, invasiveness of breast cancer (invasive or ductal carcinoma in situ [DCIS]), ovarian cancer type (serous or non-serous) (Peres et al., 2019), and uterine cancer type (endometrial; type I or type II endometrial) (Clarke et al., 2019).

2.4. Covariates

All the included covariates were assessed at baseline. These include self-reported demographic characteristics (age, race and ethnicity, educational attainment, and household income), reproductive history (age at menarche, age at first birth, breastfeeding duration, menopausal status, parity, oral contraceptive use, and hormone replacement therapy use), and relevant lifestyle factors such as smoking status and alcohol consumption. Information on recreational physical activity in the past 12 months including type, frequency, and duration was used to calculate metabolic equivalent (MET)-hours (Ainsworth et al., 2000). We collected self-reported urbanicity and evaluated neighborhood deprivation using Area Deprivation Index (Singh, 2003) for the participant's residential address. BMI was calculated using examiner measured height and weight. Detailed information on data collection and questionnaires can be found on the Sister Study website (The Sister Study: For Researchers, 2022).

2.5. Statistical analysis

Descriptive analyses of covariates including means and standard deviations were presented by breast, ovarian, and uterine cancer outcomes. Pairwise correlations were estimated for frequency of PCP use within and across four *a priori* identified product groups (i.e., beauty, hair, hygiene, and skincare), and between PCP use and covariates using Spearman's rank correlation coefficients.

The joint effects (φ) of PCP use on hormone-sensitive cancers were estimated using quantile-based g-computation with the underlying models as Cox proportional hazards regressions and age as the timescale. Participants were considered at-risk from age at enrollment until the earliest age of occurrence of the hormone-sensitive cancer diagnosis, gynecological surgery relevant to the specific outcome being analyzed (i.e., oophorectomy for ovarian cancer analysis and hysterectomy for uterine cancer analysis), last follow-up, or death. To evaluate the contribution of individual products in each of the mixtures, independent effect sizes (β) and weights (w) of d products estimated from the underlying Cox models were presented. Briefly, β_j is given as the independent effect size of product j (where $\sum_{j=1}^{d}\beta_j$ equals to φ) and w_k is given as a weight for product k among d products with the same directionality (where $w_k = \beta_k / \sum_j^d \beta_j$) (Keil et al., 2020). We estimated joint effects of products in each group that were positively but not negatively correlated, where joint effects may be of little relevance to use patterns. Cox proportional hazards regressions were also used to estimate the associations between use of single products and hormone-sensitive cancers.

The five-level frequency categories of PCP use were treated as continuous variables in all of our analyses, assuming an approximate linear relationship and uniform change in the hazard for each increase in the frequency measure. More specifically, the ordinal values based on usage frequency instead of quantiles was used in quantile-based g-computation. We further examined potential non-linearity by conducting a Wald test for a quadratic term of frequency of PCP use. The proportional hazards assumption of Cox models was evaluated by assessing correlations between the scaled Schoenfeld residuals and time using goodness-of-fit tests combined with visual inspections of the residual plots. A global test of fit was performed to assess the proportional hazards assumption for quantile-based g-computation models.

We determined potential confounders based on the previous literature and evaluating relationships between the covariates, PCP use, and outcomes from bivariate analyses. All models were adjusted for race and ethnicity (Black or African American including Black Hispanic/Latina, Hispanic/Latina non-Black, non-Hispanic White/Latina, and all others, including Asian/Pacific Islander or American Indian; as a proxy for unmeasured social constructs), educational attainment (high school or less, some college, college and above), annual household income (<$50,000, $50,000-<$100,000, ≥$100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (MET-hours per week, continuous, linear), BMI (kg/m^2, continuous, restricted cubic spline), and a product term between BMI and menopausal status at enrollment to account for opposing roles of BMI in hormone-sensitive cancer development before and after menopause (Carmichael & Bates, 2004; Qureshi et al., 2020). We used the Benjamini-Hochberg procedure to correct for multiple comparisons only for the analyses estimating the effects of single products (Benjamini & Hochberg, 1995).

We evaluated the joint effect of PCP use and hormone-sensitive cancers by menopausal status and cancer subtypes. For analyses by menopausal status, participants who transitioned from pre- to postmenopause during follow-up were censored for premenopausal cancer at age of menopause, at which time they were considered at-risk for postmenopausal cancer. Person-time after age at menopause was considered postmenopausal cancer risk time. *P*-values for heterogeneity (*p*-for-heterogeneity) by menopausal status and cancer subtypes were estimated using Wald tests of outcome-by-product interaction terms from joint adjusted models (Xue et al., 2013). Stratum-specific hazard ratios (HRs) for race and ethnicity and BMI were estimated by augmenting our primary model with modifier-by-product interaction terms, and heterogeneity was tested using Wald tests on the interaction terms. Race-specific HRs were only calculated for Black and non-Hispanic White but not for other racial and ethnic groups due to limited sample sizes.

For sensitivity analysis, we first restricted the outcomes to only medically confirmed cases. We then evaluated whether age at menarche, age at first birth, parity, breastfeeding duration, Area Deprivation Index, and urbanicity confounded the associations between PCP use and hormone-sensitive cancers by additional adjustment. We considered the significant level an alpha <0.05 to determine statistical significance for the mixture models, and a Benjamini-Hochberg multiple comparison corrected *p*-value <0.05 for the single-product models. Complete case analysis was done given the low percentage (3–5%) of missing data agglomerated over all analytic variables for each model. All analyses were conducted in R version 4.2.1.

3. Results

After an average of 11.6 years of follow-up, 4 226 breast cancer, 277 ovarian cancer, and 403 uterine cancer cases were identified in the this study. Participant characteristics by whether they were included or excluded for each cancer analyses are detailed in Table 1 & S1. Among 49 578 participants in the breast cancer analyses, 8% self-reported as Black, over 84% as non-Hispanic White, and less than 8% as Hispanic and other races and ethnicities. Approximately one-third of the participants had annual household income of more than $100 000 and more than half had at least a college education.

The correlation coefficient matrix between frequency categories of PCP use is presented in Fig. 1 and Table S2. We observed positive correlation coefficients between products within beauty, hygiene, and skincare product mixtures with beauty products showing generally higher correlations. Spearman correlation coefficients (r_s) ranged from 0.23 to 0.57 for eyeliner, eyeshadow, foundation, lipstick, mascara, and makeup remover; r_s was 0.91 between nail polish and nail polish remover. Higher correlations were also observed between different types of talc use (r_s=0.34–0.50). Due to the weaker and in some cases inverse correlation coefficients between frequency of hair products use, we did not estimate the joint effect of hair products with hormone-sensitive cancers (i.e, we did not consider hair products as a mixture that people use together).

Fig. 2 and Table S3 show the Spearman correlation coefficients

Table 1
Descriptive statistics of breast, ovarian, and uterine cancer cases and non-cases in the Sister Study (enrolled 2003–2009).

Characteristics	Eligible cohort for breast cancer analysis (n=49578)[a]		Eligible cohort for ovarian cancer analysis (n=40610)[b]		Eligible cohort for uterine cancer analysis (n=33976)[c]	
	Case (n=4226)	Non-case (n=45352)	Case (n=277)	Non-case (n=40333)	Case (n=403)	Non-case (n=33573)
Age at baseline (year); mean (SD)	57.0 (8.80)	55.6 (8.97)	57.6 (8.66)	54.9 (8.99)	57.7 (8.16)	54.2 (8.94)
Follow-up time (year); mean (SD)	6.44 (3.85)	12.1 (2.70)	6.36 (3.73)	11.7 (3.18)	6.82 (3.83)	11.6 (3.34)
Race and ethnicity; n (%)						
Black	338 (8.0%)	3924 (8.7%)	24 (8.7%)	3402 (8.4%)	33 (8.2%)	2498 (7.4%)
Hispanic non-Black	144 (3.4%)	2076 (4.6%)	8 (2.9%)	1842 (4.6%)	16 (4.0%)	1498 (4.5%)
Non-Hispanic White	3635 (86.0%)	38159 (84.1%)	240 (86.6%)	34046 (84.4%)	347 (86.1%)	28727 (85.6%)
Other[d]	108 (2.6%)	1189 (2.6%)	5 (1.8%)	1039 (2.6%)	7 (1.7%)	847 (2.5%)
Annual household income; n (%)						
<$50,000	1068 (25.3%)	11613 (25.6%)	80 (28.9%)	9774 (24.2%)	116 (28.8%)	7515 (22.4%)
$50,000-$100,000	1709 (40.4%)	18598 (41.0%)	116 (41.9%)	16478 (40.9%)	166 (41.2%)	13728 (40.9%)
≥$100,000	1449 (34.3%)	15141 (33.4%)	81 (29.2%)	14081 (34.9%)	121 (30.0%)	12330 (36.7%)
Educational attainment; n (%)						
High school or less	617 (14.6%)	6988 (15.4%)	53 (19.1%)	5826 (14.4%)	49 (12.2%)	4479 (13.3%)
Some college	1335 (31.6%)	15352 (33.9%)	95 (34.3%)	13117 (32.5%)	126 (31.3%)	10365 (30.9%)
College or above	2273 (53.8%)	23004 (50.7%)	129 (46.6%)	21383 (53.0%)	228 (56.6%)	18723 (55.8%)
Area Deprivation Index (percentile); mean (SD)	33.1 (24.3)	34.3 (24.5)	33.3 (24.3)	33.5 (22.6)	32.7 (23.6)	32.1 (24.1)
Urbanicity						
Urban	819 (19.4%)	8729 (19.2%)	43 (15.5%)	7807 (19.4%)	86 (21.3%)	6462 (19.2%)
Suburban, small town, other	2600 (61.5%)	27099 (59.8%)	180 (65.0%)	24454 (60.6%)	242 (60.0%)	20652 (61.5%)
Rural	804 (19.0%)	9427 (20.8%)	52 (18.8%)	7991 (19.8%)	75 (18.6%)	6400 (19.1%)
Alcohol consumption; n (%)						
Never or past	802 (19.0%)	8575 (18.9%)	65 (23.5%)	7153 (17.7%)	74 (18.4%)	5523 (16.5%)
Current < 1 drink/day	2811 (66.6%)	30590 (67.5%)	182 (65.7%)	27490 (68.2%)	277 (68.7%)	23123 (68.9%)
Current ≥ 1 drinks/day	609 (14.4%)	6108 (13.5%)	30 (10.8%)	5624 (13.9%)	52 (12.9%)	4870 (14.5%)
Smoking status; n (%)						
Never	2287 (54.1%)	25556 (56.4%)	143 (51.6%)	22879 (56.7%)	214 (53.1%)	19172 (57.1%)
Past or current	1939 (45.9%)	19783 (43.6%)	134 (48.4%)	17444 (43.3%)	189 (46.9%)	14392 (42.9%)
Parity; n (%)						
0–1	1408 (33.3%)	14708 (32.4%)	101 (36.5%)	13263 (32.9%)	146 (36.2%)	11665 (34.7%)
2	1554 (36.8%)	16685 (36.8%)	92 (33.2%)	14908 (37.0%)	152 (37.7%)	12332 (36.7%)
3	1264 (29.9%)	13927 (30.7%)	83 (30.0%)	12137 (30.1%)	104 (25.8%)	9554 (28.5%)
Age at first birth (year); n (%)						
Nulliparous	776 (18.4%)	8195 (18.1%)	60 (21.7%)	7456 (18.5%)	90 (22.3%)	6683 (19.9%)
<23	1293 (30.6%)	14518 (32.0%)	101 (36.5%)	11878 (29.4%)	118 (29.3%)	8496 (25.3%)
23–27	1016 (24.0%)	10595 (23.4%)	59 (21.3%)	9346 (23.2%)	108 (26.8%)	7668 (22.8%)
≥27	1141 (27.0%)	11998 (26.5%)	56 (20.2%)	11618 (28.8%)	86 (21.3%)	10696 (31.9%)
Menopausal status at baseline; n (%)						
Premenopausal	1270 (30.1%)	15186 (33.5%)	90 (32.5%)	16376 (40.6%)	114 (28.3%)	14025 (41.8%)
Postmenopausal	2956 (69.9%)	30152 (66.5%)	187 (67.5%)	23946 (59.4%)	289 (71.7%)	19538 (58.2%)
Oral contraceptive use; n (%)						
None	692 (16.4%)	7214 (15.9%)	48 (17.3%)	6245 (15.5%)	91 (22.6%)	5085 (15.1%)
<2 years	632 (15.0%)	7191 (15.9%)	60 (21.7%)	6174 (15.3%)	81 (20.1%)	4932 (14.7%)
2-<10 years	1810 (42.8%)	19471 (42.9%)	119 (43.0%)	17286 (42.9%)	167 (41.4%)	14316 (42.6%)
≥10 years	1089 (25.8%)	11427 (25.2%)	50 (18.1%)	10586 (26.2%)	63 (15.6%)	9210 (27.4%)
Hormone replacement therapy use[e]; n (%)						
None	2220 (52.5%)	25211 (55.6%)	135 (48.7%)	25630 (63.5%)	261 (64.8%)	22559 (67.2%)
Estrogen alone	814 (19.3%)	8874 (19.6%)	56 (20.2%)	4320 (10.7%)	36 (8.9%)	2296 (6.8%)
Estrogen plus Progestin	1184 (28.0%)	11135 (24.6%)	86 (31.0%)	10275 (25.5%)	104 (25.8%)	8637 (25.7%)
Age at menarche (year); n (%)						
<12	3290 (77.9%)	36130 (79.7%)	216 (78.0%)	32385 (80.3%)	302 (74.9%)	27278 (81.2%)
≥12	931 (22.0%)	9182 (20.2%)	61 (22.0%)	7915 (19.6%)	101 (25.1%)	6266 (18.7%)
Breast feeding duration (month); n (%)						
<48	3125 (73.9%)	33127 (73.0%)	223 (80.5%)	28851 (71.5%)	316 (78.4%)	23472 (69.9%)

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Eligible cohort for breast cancer analysis (n=49578)[a]		Eligible cohort for ovarian cancer analysis (n=40610)[b]		Eligible cohort for uterine cancer analysis (n=33976)[c]	
	Case (n=4226)	Non-case (n=45352)	Case (n=277)	Non-case (n=40333)	Case (n=403)	Non-case (n=33573)
≥48	1095 (25.9%)	12162 (26.8%)	53 (19.1%)	11429 (28.3%)	86 (21.3%)	10056 (30.0%)
Physical activity (metabolic equivalent MET-hours/week); mean (SD)	49.7 (31.0)	50.8 (31.4)	54.4 (37.5)	50.7 (31.2)	47.0 (32.4)	50.8 (31.3)
Body mass index (kg/m^2); mean (SD)	28.2 (6.29)	27.7 (6.24)	28.3 (6.22)	27.5 (6.18)	30.7 (7.41)	27.2 (6.11)

SD: standard deviation.

[a] Excluded women who withdrew (n=4), were diagnosed with breast cancer before baseline (n=59), had an uncertain breast cancer history (n=5), had an unclear timing of diagnosis relative to enrollment (n=17), did not contribute any follow-up time (n=287), did not respond all questions about personal care product (n=931). Missing: race and ethnicity (n=5), educational attainment (n=9), Area Deprivation Index (n=956), urbanicity (n=100), alcohol consumption (n=83), smoking status (n=13), parity (n=32), age at first birth (n=46), menopausal status (n=7), oral contraceptive use (n=52), hormone replacement therapy use (n=140), age at menarche (n=45), breast feeding duration (n=69), physical activity (n=417), body mass index (n=15).

[b] Excluded women who withdrew (n=4), were diagnosed with ovarian cancer before baseline (n=204), had an uncertain uterine cancer history (n=13), had an unclear timing of diagnosis relative to enrollment (n=30), had a bilateral oophorectomy prior to enrollment (n=8998), did not contribute any follow-up time (n=233), or did not respond all questions about personal care product use (n=792). Missing: race and ethnicity (n=4), educational attainment (n=7), Area Deprivation Index (n=749), urbanicity (n=83), alcohol consumption (n=66), smoking status (n=10), parity (n=26), age at first birth (n=36), menopausal status (n=4), oral contraceptive use (n=42), hormone replacement therapy use (n=108), age at menarche (n=33), breast feeding duration (n=54), physical activity (n=330), body mass index (n=11).

[c] Excluded women who withdrew (n=4), were diagnosed with uterine cancer before baseline (n=381), had an uncertain uterine cancer history (n=12), had an unclear timing of diagnosis relative to enrollment (n=55), had a hysterectomy prior to enrollment (n=15599), did not contribute any follow-up time (n=183), or did not respond all questions about personal product use (n=674). Missing: race and ethnicity (n=3), educational attainment (n=6), Area Deprivation Index (n=595), urbanicity (n=59), alcohol consumption (n=57), smoking status (n=9), parity (n=23), age at first birth (n=31), menopausal status (n=4), oral contraceptive use (n=31), hormone replacement therapy use (n=83), age at menarche (n=29), breast feeding duration (n=46), physical activity (n=270), body mass index (n=11).

[d] Other including Asian/Pacific Islander (26–31%), American Indian (7%), other (61–68%), and unknown (0.5%).

[e] For the breast and ovarian cancer analyses, the women who ever reported using estrogen plus Progestin hormone replace therapy were categorized as estrogen plus Progestin. For uterine cancer analysis, the women who ever reported using estrogen alone hormone replace therapy were categorized as estrogen alone.

matrix between frequency of PCP use and characteristics of study participants. Overall, PCP use was correlated with age, race and ethnicity, income, menopausal status, and BMI. Women who were older and postmenopausal at enrollment used most PCPs less frequently, except for some products such as lipstick. Black women more frequently used hair food, pomade, douche, baby oil, and petroleum jelly, and non-Hispanic White women more frequently used blush, mascara, hair spray, hair styling products, and self-tanner than other races and ethnicities. Positive correlations were mostly observed between income and beauty, hair, and skincare products, and BMI and hygiene products.

Table 2 and Figs. 3-5 show the joint effects of a one-frequency increase in use of PCP mixtures on hormone-sensitive cancers. In the adjusted quantile-based g-computation, the beauty mixture was positively associated with breast cancer (HR=1.05, 95%CI=0.99, 1.12) with the top three drivers being artificial nails (weight=26.5%), nail polish remover (weight=15.1%) and mascara (weight=15.0%) (Table S4). Moreover, the beauty product mixture showed positive associations of similar magnitude with ovarian (HR=1.08, 95%CI=0.85, 1.37) and uterine cancer (HR=1.08, 95%CI=0.88, 1.34) to those observed for breast cancer; however, the confidence intervals were wider (Figs. 4 & 5). For the hygiene mixture, we observed a positive association with ovarian cancer incidence (HR=1.35, 95%CI=1.00, 1.83), with douche as the most important component (weight=57.6%) (Table S4). In contrast, an inverse association was found between the skincare mixture and breast cancer incidence (HR=0.91, 95%CI=0.83, 0.99) with self-tanner (weight=24.9%), baby oil (weight=20.9%), and age spot lightener (weight=18.1%) as the most important contributors (Fig. 5 & Table S4). We observed use of the beaty mixture positively associated with postmenopausal breast cancer (HR=1.08, 95%CI=1.01, 1.16) but not premenopausal breast cancer cases (HR=0.90, 95%CI=0.76, 1.07) with a *p*-for-heterogeneity=0.05 (Table 2).

Results for the adjusted single-product models are shown in Figs. 3-5 & Table S5. No associations were statistically significant after adjusting for multiple comparisons. However, some associations were observed for a one-frequency increase in use of some PCPs. For example, for breast cancer, inverse associations were observed for use of talc under arm (HR=0.96, 95%CI=0.92, 0.99) and baby oil (HR=0.96, 95%CI=0.93, 1.00); an elevated hazard was found for deodorant (HR=1.03, 95% CI=1.00, 1.07). We observed a stronger positive association between douche and ovarian cancer incidence (HR=1.31, 95%CI=1.06, 1.63). For uterine cancer, elevated hazards for cuticle cream (HR=1.15, 95% CI=1.03, 1.29) and petroleum jelly (HR=1.10, 95%CI=1.01, 1.20) were observed.

We observed an elevated association between the beauty mixture and breast cancer among non-Hispanic White women but not Black women (non-Hispanic White HR=1.08, 95%CI=1.01, 1.15; Black HR=0.85, 95%CI=0.68, 1.05; *p*-for-heterogeneity=0.04; Table 3). In contrast, the association of the beauty mixture with ovarian cancer was evident for Black women but not for non-Hispanic White women (Black HR=3.62, 95%CI=1.55, 8.46; non-Hispanic White HR=0.95, 95% CI=0.72, 1.24; *p*-for-heterogeneity<0.01). When stratifying the joint effects by BMI (Table 4), stronger positive associations for the hygiene and skincare mixtures with ovarian cancer were observed in women with a BMI <25 kg/m^2 compared to those with a BMI equal or above 25 kg/m^2 (*p*-for-heterogeneity≤0.01 [hygiene], 0.03 [skincare]).

We did not observe non-linear relationships or violation of Cox proportional hazard assumption. Comparable joint effects were observed when restricting breast cancer cases to ER+ or invasive disease, whereas wider confidence intervals were present for ER- and *in* situ cancers (Table S6). A borderline significance for heterogeneity (*p*-value=0.07) by ER status was found for the association between the beaty mixture and breast cancer (ER+ HR=1.04, 95%CI=0.97, 1.12; ER- HR=0.88, 95%CI=0.73, 1.04). We also observed similar effects of the PCP mixtures on serous and all ovarian cancers, and on endometrial cancer, type 1 endometrial cancer, and all uterine cancer cases. In sensitivity analyses, we did not observe a major departure when limiting

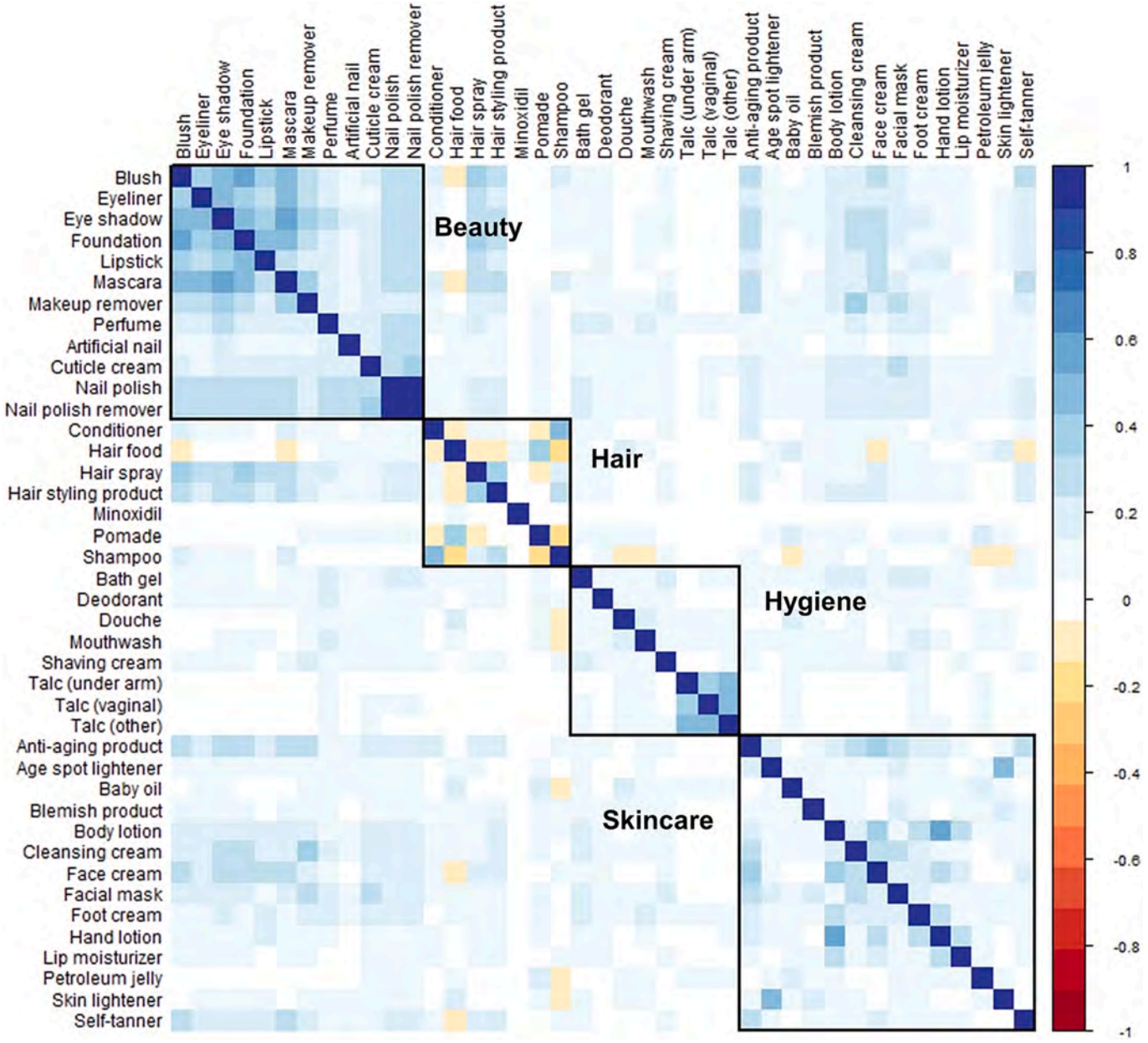

Fig. 1. Spearman correlation coefficient matrix for frequency of personal care product use.

to medically confirmed cases although associations between the beauty mixture and breast cancer and between the hygiene mixture and ovarian cancer were slightly attenuated (Table S7). When further adjusting for potential confounders such as other reproductive-related variables, Area Deprivation Index, and urbanicity, our results remain unchanged (Table S8).

4. Discussion

In this large U.S.-wide prospective cohort study, we observed joint effects of the hygiene mixture on ovarian cancer and the beauty mixture on postmenopausal breast cancer. We also found an inverse association between the skincare mixture and breast cancer. No statistically significant association between individual PCP and hormone-sensitive cancers was observed after correcting for multiple comparisons. To our knowledge, this is the first study to consider the joint effect of everyday PCP mixtures on hormone-sensitive cancers.

Taylor et al. (2018) estimated associations between PCP use and breast cancer incidence in the Sister Study (with follow-up through June 2014) using latent class analysis (LCA) combined with Cox proportional hazard models (Taylor et al., 2018). With an additional six years of follow-up and over 1 900 more breast cancer cases, our current results were mostly consistent with the previously reported findings, particularly the relationship between increased use of beauty products and a higher postmenopausal breast cancer incidence. Our results differ however with regards to the skincare mixture. Taylor et al., observed an elevated association whereas we observed an inverse association between the skincare mixture and breast cancer. This discrepancy can be partly explained by the different statistical approaches used in these two studies. While quantile-based g-computation estimates the joint effect of one-frequency level increase in all the PCPs included in the mixture, the approach combining LCA with Cox proportional hazard regression estimates the associations between the groups of women with different exposure profiles and incident breast cancer. Notably, some hygiene products positively contributing to breast cancer in the current analyses such as deodorant and shaving cream or some skincare products

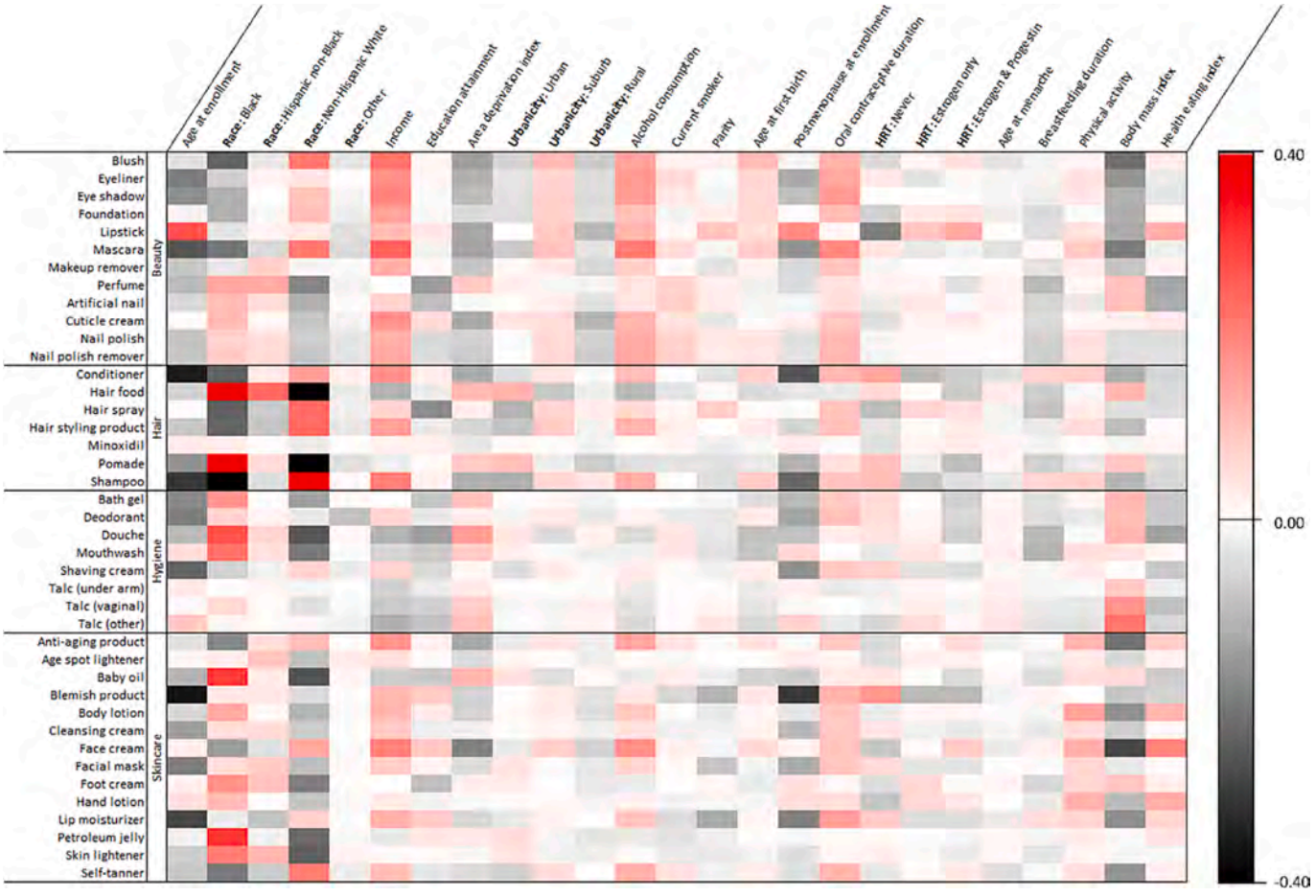

Fig. 2. Spearman correlation coefficients for frequency of personal care product use and covariates. [Note: Race and ethnicity, urbanicity, and HRT were coded as binary covariates for each category.]

inversely associated with breast cancer such as age spot lightener, baby oil, lip moisturizer, and self-tanner were not included in Taylor et al.'s LCA-based grouping due to a lack of variability in posterior probability of these products across the groups.

Results from previous studies investigating associations between everyday PCP use and hormone-sensitive cancers have focused on use of individual products, including associations for deodorant with breast cancer (Allam, 2016; Linhart et al., 2017; Mousavi & Vaghar, 2021) and talc and douche with ovarian (Gonzalez et al., 2016; Goodman et al., 2020; Penninkilampi & Eslick, 2018; Wentzensen & O'Brien, 2021) and uterine cancer (O'Brien et al., 2019, 2021). Similar to some previous studies (Allam, 2016; Mousavi & Vaghar, 2021), the elevated association between deodorant use and breast cancer was modest and not statistically significant in the single-product models, moreover, no evidence of a positive association between the hygiene mixture (containing deodorant) and breast cancer was observed. We observed a positive association for the hygiene mixture in relation to incident ovarian cancer with douche and genital use talc as the most important contributors to the mixture, which is consistent with the findings from both the Sister Study (Gonzalez et al., 2016) and other studies (Penninkilampi & Eslick, 2018; Wentzensen & O'Brien, 2021). Some previous studies have also demonstrated positive associations between talc use and uterine/endometrial cancer (O'Brien et al., 2019, 2021). We observed similar relationships of talc use in single-product models and the hygiene mixture use (under arm and genital talc use as the primary contributors) in multi-product models with uterine cancer incidence, although the confidence intervals were wide.

While our findings showed an inverse association between the skincare mixture and breast cancer incidence, previous studies have not found an association of individual skincare products such as skin lightener (Brinton et al., 2018), body lotion, hand cream, and facial cream (Rylander et al., 2019) with breast or endometrial cancer. Although it is possible that using skincare products may reduce risk of breast cancer, this association could also be due to residual confounding. For instance, women who frequently use skincare product may also engage in other health-seeking behaviors, which could reduce their risk of breast cancer development. However, we did not observe meaningful changes in the estimates after adjusting for additional confounders such as physical activity, smoking status, and alcohol consumption.

We observed heterogeneous associations for the beauty mixture with breast cancer and with ovarian cancer among Black and non-Hispanic White participants. Since chemical composition of products may vary based on whether they are marketed towards women of different races and ethnicities, the estimated effects for the PCP mixtures could vary. For example, women likely select different colors and levels of UV protection of cosmetic products based on their skin tone, resulting in different chemical exposures from the same type of products (Collins et al., 2021; Zota & Shamasunder, 2017). Moreover, different frequency of use within the same frequency category by Black and non-Hispanic White women could also contribute to heterogeneity. It is possible that Black women in the highest frequency category (i.e., reported using a product "more than 5 times per week") used certain products more frequently than non-Hispanic White women, or vice versa. In this study, we found that Black women used perfume, artificial nails, cuticle nail,

Table 2
Associations between one-frequency category increase in use of multiple personal care products and all, premenopausal, and postmenopausal breast, ovarian, and uterine cancer using quantile-based g-computation.

	All				Premenopausal cancer				Postmenopausal cancer				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	p_{het}[c]
Breast cancer													
Beauty	549283	43052/ 4036	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)	94550	15329/ 580	0.92 (0.78, 1.08)	0.90 (0.76, 1.07)	454721	40367/ 3419	1.08 (1.02, 1.16)	1.08 (1.01, 1.16)	0.05
Hygiene	559255	43888/ 4109	1.02 (0.94, 1.12)	1.01 (0.92, 1.10)	95357	15471/ 579	1.03 (0.80, 1.32)	1.14 (0.88, 1.48)	463887	41175/ 3493	1.03 (0.94, 1.14)	1.00 (0.91, 1.11)	0.37
Skincare	554257	43462/ 4074	0.89 (0.82, 0.97)	0.91 (0.83, 0.99)	94931	15380/ 577	0.93 (0.75, 1.15)	0.92 (0.73, 1.14)	459314	40765/ 3460	0.90 (0.81, 0.99)	0.93 (0.84, 1.02)	0.67
Ovarian cancer													
Beauty	453436	38403/ 264	1.09 (0.86, 1.37)	1.08 (0.85, 1.37)	95950	15896/ 20	0.87 (0.32, 2.41)	1.04 (0.36, 3.00)	357474	34695/ 231	1.08 (0.84, 1.39)	1.05 (0.81, 1.37)	0.95
Hygiene	461152	39092/ 267	1.49 (1.12, 1.99)	1.35 (1.00, 1.83)	96767	16038/ 21	1.77 (0.75, 4.20)	1.54 (0.61, 3.91)	364374	35360/ 233	1.49 (1.07, 2.06)	1.35 (0.97, 1.89)	0.90
Skincare	457130	38727/ 267	0.86 (0.59, 1.26)	0.84 (0.57, 1.25)	96420	15960/ 20	1.39 (0.49, 3.96)[d]	1.54 (0.52, 4.58)[d]	360786	35011/ 234	0.82 (0.53, 1.28)	0.80 (0.51, 1.27)	-[e]
Uterine cancer													
Beauty	375632	32031/ 377	1.04 (0.85, 1.27)	1.08 (0.88, 1.34)	80775	13651/ 22	0.73 (0.30, 1.82)	0.65 (0.25, 1.66)	294857	28448/ 338	1.04 (0.84, 1.29)	1.10 (0.88, 1.37)	0.28
Hygiene	381491	32559/ 390	1.27 (0.96, 1.68)	1.06 (0.79, 1.42)	81364	13758/ 23	0.99 (0.27, 3.68)	0.50 (0.11, 2.16)	300127	28942/ 351	1.31 (0.98, 1.76)	1.12 (0.83, 1.52)	0.30
Skincare	378382	32275/ 384	0.88 (0.66, 1.17)	1.09 (0.81, 1.46)	81077	13688/ 22	0.81 (0.24, 2.77)	0.91 (0.25, 3.34)	297305	28676/ 346	0.88 (0.65, 1.19)	1.10 (0.80, 1.50)	0.94

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] Accounted for age by using age as the timescale.

[b] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal); menopausal status at enrollment were excluded in premenopausal and postmenopausal models.

[c] *P*-for-heterogeneity estimated by Wald tests of outcome-by-hair-product interaction terms from joint adjusted models.

[d] Remove product age spot lightener and skin lightener due to low case counts in some frequency categories (including these products yield infinite confidence intervals).

[e] Unable to estimate *p*-for-heterogeneity due to different products included in the mixture for premenopausal and postmenopausal analyses.

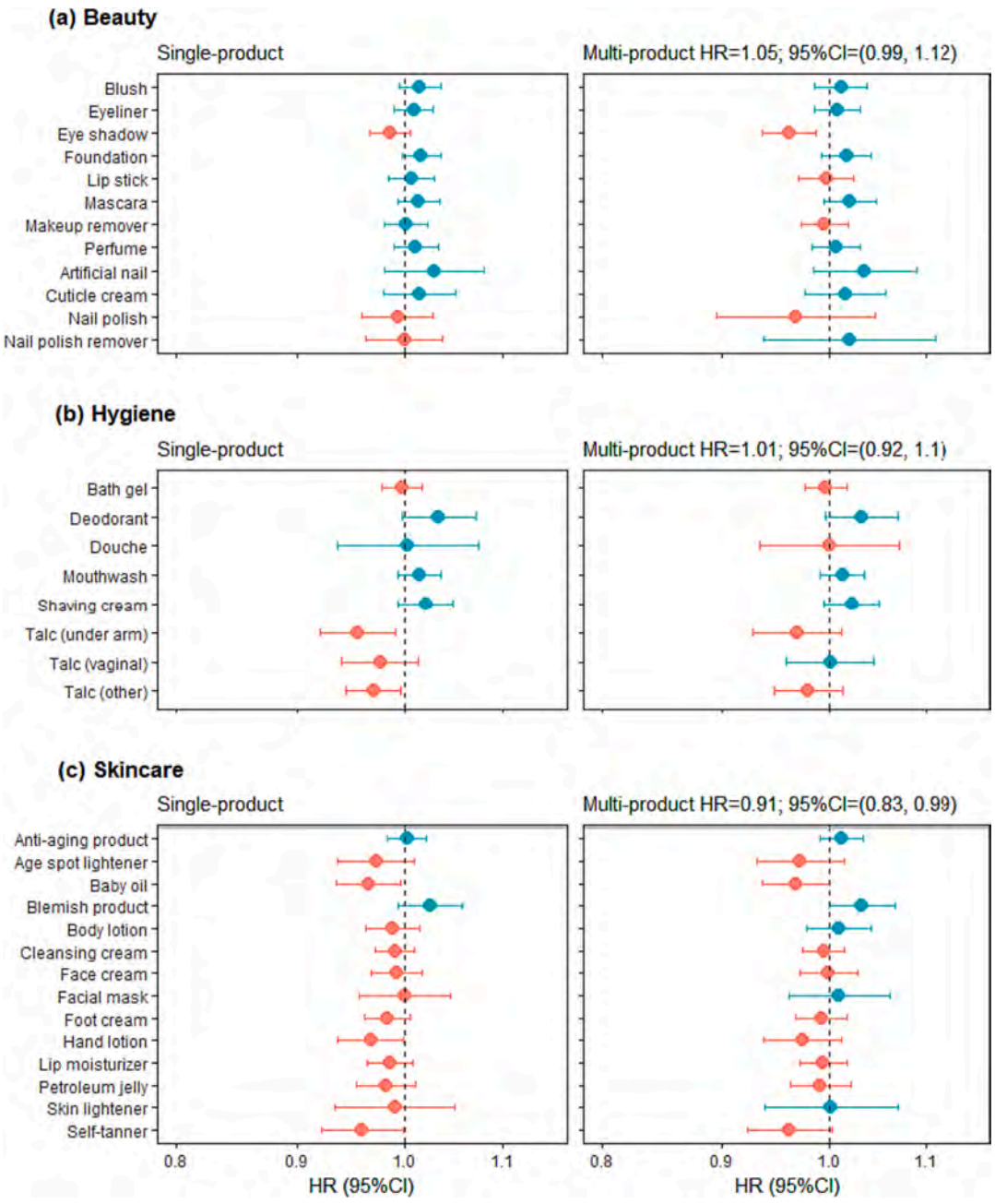

Fig. 3. Adjusted associations between one-frequency category increase in use of personal care products and breast cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

and nail polish remover more frequently than non-Hispanic White participants. Given these products are the primary positive contributors within the beauty mixture to ovarian cancer incidence, this may partly explain why the effect of the beauty mixture on ovarian cancer appears to be stronger in Black women.

Our findings provide some evidence showing that EDC exposure from PCPs may play a role in the etiology of hormone-sensitive cancers, with the positive association between the beauty mixture and breast cancer incidence only identified in postmenopausal women. Additionally, the hygiene and skincare mixtures exhibit stronger positive associations with ovarian cancer among leaner women. These observations are consistent with previous studies indicating a greater impact of exogenous hormone exposure in a relatively low hormone environment (Calle & Kaaks, 2004; Huang et al., 1997; Simpson, 2003; Tworoger et al., 2005). Specifically, environmental EDCs (Parada et al., 2019) and hormone replacement therapy (Green et al., 2012; Riman et al., 2001) have been shown to have a stronger effect on breast cancer in women with low BMI and in their postmenopausal years. However, as

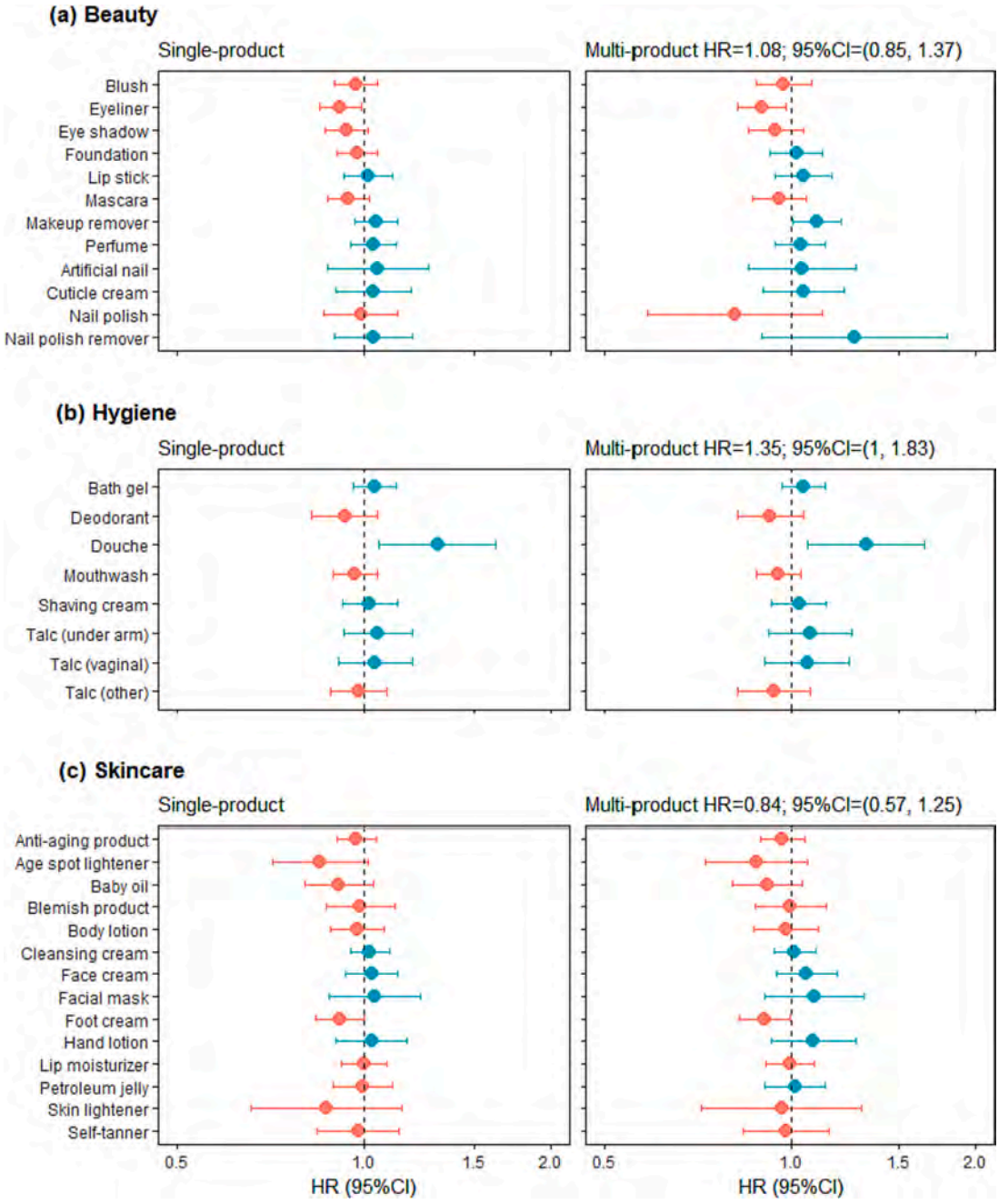

Fig. 4. Adjusted associations between one-frequency category increase in use of personal care products and ovarian cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

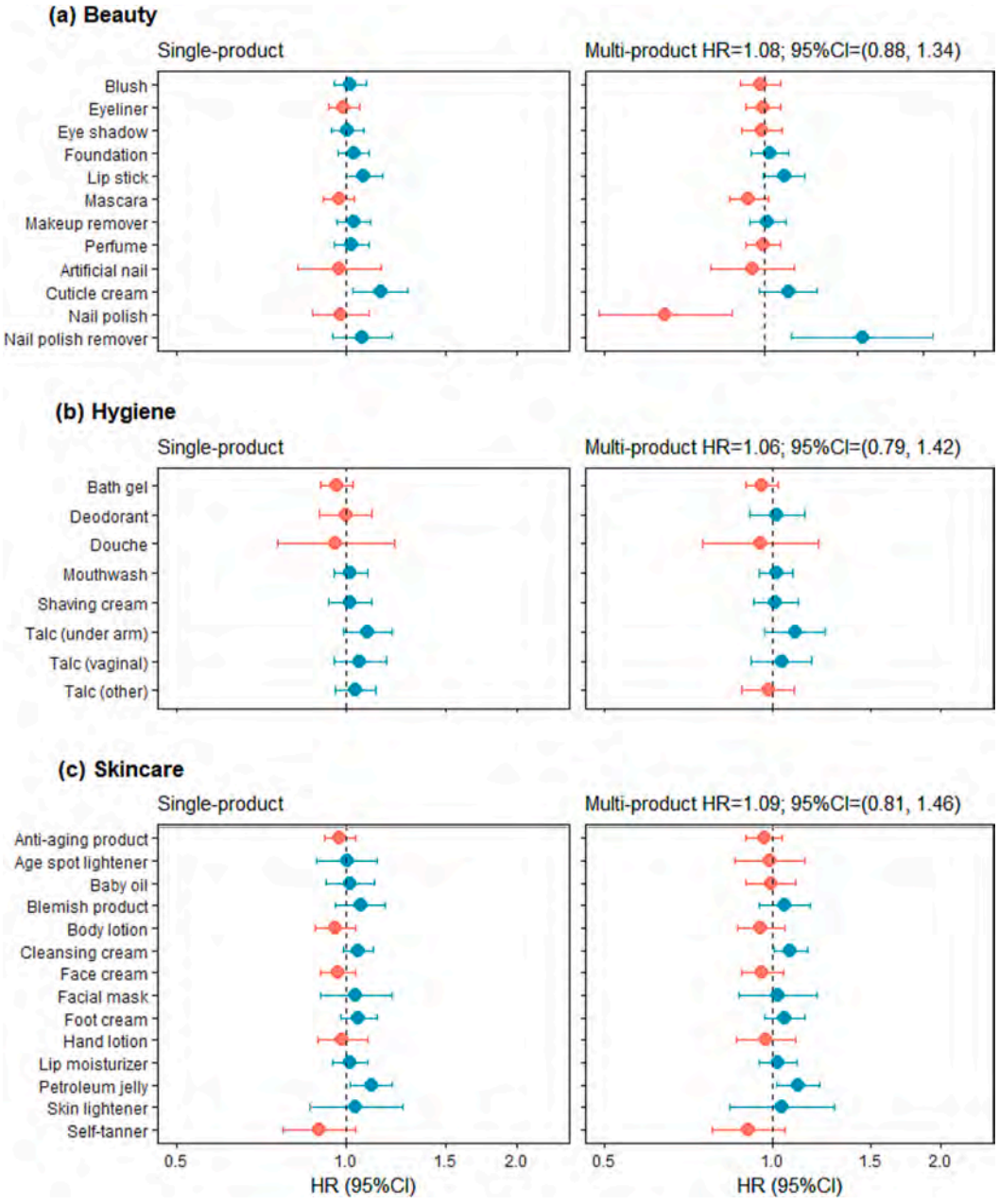

Fig. 5. Adjusted associations between one-frequency category increase in use of personal care products and uterine cancer: comparison of effect estimates from single-product models (evaluating products individually) using Cox proportional hazards models and effect estimates from the underlying models of multi-product analyses (evaluating products together) using quantile-based g-computation. HR: hazard ratio; 95%CI: 95% confidence interval. Colors of the forest plots only show the directionality of HRs and did not suggest associations or statistical significance. Models used age as the timescale and adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

Table 3
Associations between one-frequency category increase in use of multiple personal care products and breast, ovarian, and uterine cancer by Black and non-Hispanic White women using quantile-based g-computation.

	Black[a]				Non-Hispanic White				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[b]	Fully adjusted HR (95%CI)[b,c]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[b]	Fully adjusted HR (95%CI) [b,c]	p_{het}[d]
Breast cancer									
Beauty	42107	3632/ 312	0.84 (0.68, 1.05)	0.85 (0.68, 1.05)	471716	36398/ 3483	1.08 (1.02, 1.16)	1.08 (1.01, 1.15)	0.04
Hygiene	43328	3740/ 323	0.96 (0.71, 1.29)	0.97 (0.72, 1.30)	479593	37045/ 3544	1.03 (0.93, 1.14)	1.02 (0.92, 1.13)	0.72
Skincare	42711	3686/ 317	0.75 (0.51, 1.10)	0.75 (0.51, 1.10)	475753	36722/ 3518	0.94 (0.85, 1.04)	0.97 (0.88, 1.08)	0.21
Ovarian cancer									
Beauty	34110	3156/ 23	3.67 (1.57, 8.57)	3.62 (1.55, 8.46)	389814	32561/ 230	0.96 (0.74, 1.24)	0.95 (0.72, 1.24)	<0.01
Hygiene	35065	3249/ 22	1.10 (0.40, 3.05)	1.04 (0.37, 2.92)	395931	33099/ 233	1.42 (1.01, 2.00)	1.25 (0.88, 1.78)	0.73
Skincare	34563	3202/ 23	0.88 (0.16, 4.92)	0.91 (0.16, 5.10)	392892	32822/ 233	0.56 (0.30, 1.07)	0.57 (0.30, 1.10)	0.63
Uterine cancer									
Beauty	23914	2318/ 31	1.32 (0.62, 2.83)	1.42 (0.66, 3.05)	328002	27519/ 326	0.98 (0.79, 1.23)	1.04 (0.82, 1.31)	0.44
Hygiene	24542	2380/ 32	2.35 (0.93, 5.92)	2.19 (0.86, 5.59)	332718	27936/ 338	1.04 (0.73, 1.48)	0.92 (0.64, 1.32)	0.09
Skincare	24224	2351/ 30	1.28 (0.66, 2.47)[e]	1.46 (0.75, 2.86)[e]	330321	27716/ 335	0.67 (0.43, 1.03)	0.83 (0.53, 1.30)	-[f]

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] All African American/Black including Hispanic Black.

[b] Accounted for age by using age as the timescale.

[c] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (restricted cubic spline, continuous, kg/m^2), and product term of BMI (restricted cubic spline, continuous, kg/m^2) and menopausal status at enrollment (premenopausal, postmenopausal).

[d] *P*-for-heterogeneity estimated by Wald tests on augmented race-by-product terms in the adjusted models.

[e] Remove age spot lightener, skin lightener, and self-tanner due to low case counts in some frequency categories (including these products yield infinite confidence intervals).

[f] Unable to estimate *p*-for-heterogeneity due to different products included in the mixture for Black and non-Hispanic White analyses.

Table 4
Associations between one-frequency category increase in use of multiple personal care products and breast, ovarian, and uterine cancer by body mass index (BMI) groups using quantile-based g-computation.

	BMI <25				25≤ BMI <30				BMI ≥30				
Product mixture	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI)[a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI) [a,b]	Person-time	Non-case/ case n	Age-adjusted HR (95%CI)[a]	Fully adjusted HR (95%CI) [a,b]	p_{het}[c]
Breast cancer													
Beauty	220673	17030/ 1463	1.03 (0.93, 1.15)	1.00 (0.93, 1.15)	172790	13535/ 1317	1.01 (0.91, 1.12)	1.01 (0.91, 1.12)	155820	12487/ 1256	1.10 (0.99, 1.22)	1.10 (0.99, 1.22)	0.51
Hygiene	223496	17273/ 1469	1.10 (0.94, 1.28)	1.12 (0.96, 1.30)	176022	13794/ 1354	1.07 (0.92, 1.25)	1.09 (0.93, 1.27)	159737	12821/ 1286	0.82 (0.71, 0.96)	0.83 (0.72, 0.97)	0.14
Skincare	221730	17122/ 1458	0.96 (0.83, 1.11)	0.96 (0.83, 1.11)	174429	13665/ 1339	0.89 (0.76, 1.03)	0.88 (0.75, 1.03)	158098	12675/ 1277	0.87 (0.74, 1.02)	0.86 (0.73, 1.02)	0.45
Ovarian cancer													
Beauty	190528	15785/ 93	1.19 (0.82, 1.74)	1.18 (0.80, 1.72)	140758	11953/ 81	1.37 (0.93, 2.02)	1.38 (0.93, 2.04)	122150	10665/ 90	0.69 (0.42, 1.13)	0.69 (0.42, 1.14)	0.48
Hygiene	192781	15983/ 94	2.29 (1.47, 3.56)	2.14 (1.37, 3.35)	143319	12181/ 81	0.97 (0.50, 1.86)	0.91 (0.47, 1.76)	125052	10928/ 92	1.17 (0.71, 1.93)	1.12 (0.67, 1.86)	<0.01
Skincare	191227	15847/ 94	1.33 (0.76, 2.30)	1.30 (0.74, 2.26)	142063	12064/ 83	0.63 (0.26, 1.54)	0.60 (0.25, 1.47)	123840	10816/ 90	0.46 (0.19, 1.13)	0.44 (0.18, 1.08)	0.03
Uterine cancer													
Beauty	166933	13895/ 90	1.05 (0.66, 1.68)	1.13 (0.71, 1.81)	113958	9794/ 106	1.10 (0.75, 1.63)	1.18 (0.80, 1.76)	94742	8351/ 181	0.94 (0.71, 1.25)	1.00 (0.75, 1.34)	0.77
Hygiene	168774	14067/ 92	0.89 (0.42, 1.88)	0.92 (0.44, 1.94)	115890	9965/ 110	1.22 (0.73, 2.04)	1.24 (0.74, 2.07)	96826	8527/ 188	1.01 (0.68, 1.51)	1.02 (0.68, 1.54)	0.68
Skincare	167443	13945/ 94	1.39 (0.85, 2.29)	1.50 (0.91, 2.46)	114949	9882/ 107	0.77 (0.40, 1.45)	0.84 (0.44, 1.60)	95990	8430/ 183	0.79 (0.50, 1.26)	0.85 (0.53, 1.37)	0.68

HR (95%CI): hazard ratio (95% confidence intervals); n: number; p_{het}: p-for-heterogeneity.

[a] Accounted for age by using age as the timescale.

[b] Adjusted for race and ethnicity (African American/Black, Hispanic/Latina non-Black, non-Hispanic White, other), educational attainment (high school or less, some college, college and above), income (<50,000, 50,000-<100,000, ≥100,000), menopausal status at enrollment (premenopausal, postmenopausal), smoking (never, past or current), alcohol (never or past, current <1 drink, current ≥1 drinks), oral contraceptive use duration (none, <2 years, 2-<10 years, ≥10 years), hormone replacement therapy (none, estrogen alone, estrogen plus progestin), physical activity (metabolic equivalent [MET] hours per week, continuous), BMI (<25, 25-<30, ≥30), product term of BMI (<25, 25-<30, ≥30) and menopausal status at enrollment (premenopausal, postmenopausal).

[c] *P*-for-heterogeneity estimated by Wald tests on augmented BMI-by-product terms in the adjusted models.

the similar heterogeneity was not consistently observed in every product mixture or all three hormone-sensitive cancers, more studies are necessary to further elucidate the underlying biological pathways for the relationship between PCP exposures and breast, ovarian, and uterine cancer.

Our focus on product mixtures is a strength of this analysis. While a single PCP, especially the everyday products considered here, may only have a small impact on hormone-sensitive cancer development, using multiple products could collectively have greater effects. To address this, we used quantile-based g-computation to explicitly estimate the joint effects of exposure to PCP mixtures, which may be difficult to quantify using single-product approaches. Moreover, compared to the previous LCA-based grouping, where the groups labeled as "frequent users" of products can nonetheless contain a portion of infrequent users, the effect from high exposure estimated by quantile-based g-computation could be stronger and more straightforward because the effect corresponds to frequent use of all PCPs within a mixture. Additional strengths include our large sample size, prospective study design which minimizes recall bias and reverse causation, and comprehensive questionnaire data on PCP and potential confounders.

We did not collect information on product brands or ingredients, which prevented us from directly examining the impact of specific chemicals or examining trends in products over time. However, self-reported product use may better reflect the real-world exposures to complicated chemical mixtures, which might not be disclosed by manufacturers on the labels or might be derivatives or contaminants arising during production or storage. Self-reported product use may also more accurately estimate the chronic exposure to short-lived chemicals, which would be difficult to reliably assess using biomarkers (Ahern et al., 2022; Rivera-Núñez et al., 2021). We only evaluated product use in the 12 months prior to the baseline. Although douche and genital talc use have shown to be consistently reported over time (O'Brien et al., 2023), we did not have information on other PCP use over the lifetime. In addition, given the limited case counts, particularly for ovarian and uterine cancer, the analyses for some cancer subtypes or modifications yielded wide confidence intervals.

This study utilized a sophisticated mixtures approach to examine the relationships between everyday PCPs and the incidence of hormone-sensitive cancers in a large prospective cohort in the U.S. Our findings contribute to a growing body of evidence on a possible collective effect of PCP use and breast cancer using a different analytic approach and provides novel information on associations between the PCP mixtures and ovarian and uterine cancer. Although the observed effects of a one-frequency level increase were modest in magnitude, the impact would be more substantial when comparing the most frequent users with never users. For example, an 8% higher hazard of postmenopausal breast cancer for a one-frequency level increase in the beauty mixture use could translate to approximately a 36% higher hazard for the most frequent users compared with never users. Future efforts are warranted to consider PCP exposure in relation to hormone-sensitive cancers in different populations, where patterns of use and chemicals in products may differ.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data necessary to reproduce the current analysis are publicly available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute of Health, National Institute of Environmental Health Sciences (grant number Z01ES044005, Z1AES103332). We sincerely appreciate the contributions of Sister Study participants and the study management group. We also gratefully acknowledge Drs. Danielle R. Stevens and Kemi Ogunsina for the careful review and thoughtful feedback on this manuscript.

Data Sharing

All data necessary to reproduce the current analysis are publicly available following procedures described on the Sister Study website (https://sisterstudy.niehs.nih.gov/English/data-requests.htm).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.108298.

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EXHIBIT 47

Executive Summary

Executive Summary of the Ovarian Cancer Evidence Review Conference

William Burke, MD, Joel Barkley, MD, Emily Barrows, MD, Rebecca Brooks, MD, Kimberly Gecsi, MD, Kathryn Huber-Keener, MD, PhD, Myrlene Jeudy, MD, Shirley Mei, MD, Julia Sage O'Hara, MPH, and David Chelmow, MD

The Centers for Disease Control and Prevention awarded funding to the American College of Obstetricians and Gynecologists to develop educational materials for clinicians on gynecologic cancers. The American College of Obstetricians and Gynecologists convened a panel of experts in evidence review from the Society for Academic Specialists in General Obstetrics and Gynecology and content experts from the Society of Gynecologic Oncology to review relevant literature, best practices, and existing practice guidelines as a first step toward developing evidence-based educational materials for women's health care clinicians about ovarian cancer. Panel members conducted structured literature reviews, which were then reviewed by other panel members and discussed at a virtual meeting of stakeholder professional and patient advocacy organizations in February 2022. This article is the executive summary of the relevant literature and existing recommendations to guide clinicians in the prevention, early diagnosis, and special considerations of ovarian cancer. Substantive knowledge gaps are noted and summarized to provide guidance for future research.

(Obstet Gynecol 2023;142:179–95)
DOI: 10.1097/AOG.0000000000005211

The Centers for Disease Control and Prevention funded the American College of Obstetricians and Gynecologists (ACOG) to create and disseminate educational material for clinicians on the early diagnosis and prevention of gynecologic cancers and early-onset breast cancer.[1,2] Ovarian cancer is relatively rare, ranking 17th among all cancers in the United States, with an incidence of 10.6 per 100,000 from 2015 to 2019.[3,4] However, ovarian cancer is the fifth

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Supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) under cooperative agreement number 6 NU38OT000287-04-03, which was awarded to the American College of Obstetricians and Gynecologists (ACOG).

Presented at the American College of Obstetricians and Gynecologists' Annual Clinical and Scientific Meeting, May 19–21, 2023, Baltimore, Maryland.

The authors thank Jean Riedlinger, MSLS, AHIP, Yvonnada McNeil, MSLS, and Carrie Snead, MA, for their assistance with the database searches; Dana Trevas, Nancy O'Reilly, MHS, PMP, and Apurvi Shah, MPH, for facilitating the management of the review and editing process; and the individuals who attended the February 2022 Ovarian Cancer Evidence Review Conference, listed in Appendix 1, available online at http://links.lww.com/AOG/D170.

Participation in this project as an attendee of the Evidence Review Conference does not constitute organizational or individual endorsement of the conclusions. Information in this article should not be construed as the official position or policy of, or should any endorsements be inferred by, CDC, HHS, or the U.S. government.

Each author has confirmed compliance with the journal's requirements for authorship.

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Financial Disclosure

Rebecca Brooks is a member of an AstraZeneca speakers' bureau related to ovarian cancer, a past advisory board member for Tempus, a past advisory board member and consultant for GSK and Merck & Co., Inc., and a past non-branded speaker for Clinical Care Options, CURE Educated Patient Summit, and Med Educator Consortium. Julia Sage O'Hara is an employee of the American College of Obstetricians and Gynecologists. David Chelmow is the immediate past president of ASCCP and the Council of University Chairs of Obstetrics and Gynecology, receives a stipend as the editor-in-chief of the Medscape Obstetrics and Gynecology Clinical Reference Book, and was on the American Board of Obstetrics and Gynecology Board of Directors during the evidence review period. David Chelmow is a member of the U.S. Preventive Services Task Force (USPSTF). This article does not necessarily represent the views and policies of the USPSTF. All authors except for Julia Sage O'Hara received a one-time payment from ACOG for their participation in the development of ovarian cancer educational materials. The other authors did not report any potential conflicts of interest.

ISSN: 0029-7844/23

most common cause of cancer death in women in the United States and is the deadliest form of gynecologic cancer.[5,6] Because of its high mortality rate, ovarian cancer was chosen as the second gynecologic cancer for educational material development. To ensure that these materials were based on the most current literature and guidelines, an extensive literature review was conducted. This article is the evidence summary, which is presented in detail in Appendices 2–8, available online at http://links.lww.com/AOG/D170. The health care professional educational material is available online at acog.org.

METHODS

Methods for the evidence review and educational material development closely followed the process for the early-onset breast cancer and uterine cancer projects.[1,2] The ACOG convened an expert panel to identify the best evidence and practices from the literature and existing relevant guidelines. The panel was recruited from the Society for Academic Specialists in General Obstetrics and Gynecology to review and summarize the evidence. The panel was supplemented by representatives from the Society of Gynecologic Oncology. Panel members were selected on the basis of expertise in evidence review and synthesis. The panel developed research questions and used the PICO criteria (P=patient, problem, or population; I=intervention; C=comparison, control, or comparator; O=outcome [s]) to frame the literature review (Box 1).

Experts in literature searches from the ACOG Resource Center searched the Cochrane Library, MEDLINE (through Ovid), and PubMed (for references not indexed through MEDLINE) for articles published between January 2000 and October 2021. Literature was organized by types of studies. Published guidelines were categorized separately from studies. A primary reviewer was assigned to each topic to review titles and abstracts and then the entire manuscript when appropriate. Reference lists from relevant articles found in the search were also reviewed. Reviewers did additional searches as necessary, including extending the search range. Internet searches were performed with standard search engines to seek guidelines, recommendations, and tools that might not have been published in peer-reviewed publications. Relevant information was evaluated and compiled into an evidence summary template by a primary reviewer. Completed templates were then reviewed by a secondary reviewer. The primary and secondary reviewers worked together to revise the evidence summary in response to the secondary reviewer's comments.

The ACOG convened the Ovarian Cancer Evidence Review Conference virtually on February 9–10, 2022, bringing together expert panel members and representatives from stakeholder professional and patient advocacy organizations (Appendix 1, http://links.lww.com/AOG/D170). The panel members who served as primary reviewers for each of the research topics prerecorded their presentations, which were viewed in advance by meeting participants, including the stakeholder representatives. Meeting attendees also reviewed the evidence review summaries. At the meeting, expert panel members presented a brief summary of their evidence review findings, which was followed by an open comment and discussion period with conference attendees. Comments were integrated into the evidence review summary by the primary reviewer. The revised summaries were sent to the secondary reviewer for final review, and final revisions were made by the primary reviewer (Appendices 2–8, http://links.lww.com/AOG/D170). The final evidence review summaries were used to develop the educational material (available online at acog.org).

During the performance of the review, there was significant overlap between the results of the literature searches for the research questions about risk factors and risk reduction. The appendices for these two topics present the full evidence summary for each (Appendices 3 and 4, http://links.lww.com/AOG/D170). For this executive summary, epidemiologic and retrospective studies from both searches are combined in the Risk Factors section, and the Risk Reduction section contains summaries of intervention trials and recommendations. Major professional society guidelines cited in the evidence reviews were replaced with the most current versions during the executive summary preparation.

When reporting results of individual studies, we used the terminology describing gender, race, and ethnicity from the source article. Studies almost uniformly used "women" or "females" to refer to the gender of those affected by ovarian cancer. Although ovarian cancer can affect individuals of different sexes who have ovaries, we used "women" or "females" in this review to reflect the cited literature. In keeping with the most common categories of race and ethnicity used in national data collection, when we had a choice of terminology, we used "Black" in place of "non-Hispanic Black" or "African American" and "White" in place of "non-Hispanic White" or "Caucasian." We used "Hispanic," not "Latinx," because "Latinx" was rarely used in any of the articles reviewed. Although some studies restricted their

Box 1. Research Questions and PICO Criteria Used to Frame the Literature Review*

1. Epidemiology of ovarian cancer
   a. Types of ovarian cancer: What is the incidence of ovarian cancer and whom does it affect?
   b. What is the effect of age on ovarian cancer risk? How strong are these risks (quantitate magnitude of risk, broken down by type of cancer when possible)?
2. Risk factors for ovarian cancer
   a. What lifestyle factors are risk factors for ovarian cancer? How strong are these risks?
   b. What hormonal factors are risk factors for ovarian cancer? How strong are these risks?
   c. What family health history factors are risk factors for ovarian cancer? How strong are these risks?
   d. What health history factors are risk factors for ovarian cancer? How strong are these risks?
3. Prevention and risk reduction for ovarian cancer
   a. Which interventions are effective at reducing ovarian cancer in women at average and high risk (attempt to quantify magnitude of risk reduction)?
4. Screening for ovarian cancer
   a. What is the evidence against screening asymptomatic women at average risk?
   b. Are there subgroups at high risk who benefit from screening? How can women at high risk be identified?
   c. How should screening be performed in subgroups at high risk?
5. Early detection
   a. What are common presenting symptoms among women diagnosed with ovarian cancer? How predictive are these presenting symptoms of ovarian cancer?
   b. In premenopausal patients with symptoms, who should undergo evaluation for ovarian cancer? What are the most effective methods of evaluation for ovarian cancer?
   c. In postmenopausal patients with symptoms, what are the most effective methods of evaluation for ovarian cancer?
   d. In asymptomatic patients with an incidental finding of an ovarian cyst on transvaginal ultrasonography or computed tomography, who should undergo evaluation for ovarian cancer? What are the most effective methods of evaluation for ovarian cancer?
6. Health disparities in ovarian cancer
   a. What groups experience inequities and disparities in the ovarian cancer care continuum, and what are those observed disparities?
   b. What factors contribute to health disparities in ovarian cancer?
   c. How can health disparities in ovarian cancer be mitigated so that optimal care and desirable outcomes are shared by populations experiencing health disparity?
7. Overview of diagnosis and care coordination for the primary care practitioner
   a. Unified summary of guidelines and non–guideline-driven standard of care, including
      i. Standard care evaluation of symptoms and incidentally found masses
      ii. Criteria for referral to gynecologic oncologist subspecialist
      iii. Brief summary of what will likely happen after referral at the level for primary care practitioner to set expectations and to provide anticipatory guidance for patient
8. Special considerations
   a.What special considerations do primary care practitioners need to be aware of throughout the ovarian cancer care continuum? How influential are these factors in the patient experience and outcome?

P=patient, problem, or population; I=intervention; C=comparison, control, or comparator; O=outcome(s).
*See Appendices 2–8, http://links.lww.com/AOG/D170, for PICO criteria used for each outline question.

analysis to Hispanic White individuals, others included Hispanic individuals of any race. Given the lack of consistency in the literature, we used "Hispanic" without reference to race.

EPIDEMIOLOGY AND CLASSIFICATION

High-grade serous carcinomas represent the majority of ovarian cancers; however, most do not arise from the ovary but from the fallopian tube.[7] The term "ovarian cancer" is used throughout this review and represents a constellation of malignancies involving the ovary, peritoneum, and fallopian tube.

The lifetime risk of developing ovarian cancer to age 95 years is about 1.1%. In 2018, 235,081 women in the United States were living with the disease. It is estimated that in 2022 there were 19,880 new cases in the United States.[4] An estimated 12,810 women died of ovarian cancer in the United States in 2022.[6]

Stage at diagnosis is typically advanced, with only 19% of cases localized on presentation and at least half of cases presenting with distant disease.[6] Overall 5-year survival in the United States is 49.7% and is strongly correlated with stage at the time of diagnosis. Five-year survival is 93.1%, 74.2%, 30.8%, and 28.2% when stage at the time of diagnosis is localized, regional, distant, and unstaged, respectively.[4] Recurrence risk correlates strongly with stage at diagnosis. Fewer than 10% of women with stage I disease will have recurrence, whereas 90% of women with stage IV disease will have recurrent disease.[8]

Ovarian cancers are classified by the tissue from which they originate: epithelial, germ cell, and sex cord–stromal. Epithelial cancer is by far the most common, accounting for 90% of malignant ovarian neoplasms. Germ-cell tumors represent about 5% of ovarian cancers, and sex cord–stromal tumors account for 3–5%. All of these types can be further subdivided (Box 2).[5,9–11]

New cases of ovarian cancer in the United States have been falling by an average of 3.3% each year since 2009, and age-adjusted death rates have been falling by about 2.7% annually since 2010[4] (Appendix 2, http://links.lww.com/AOG/D170, provides a complete evidence summary). Incidence and mortality by race and ethnicity are reviewed in detail in the companion article, "Health Disparities in Ovarian Cancer: Report from the Ovarian Cancer Evidence Review Conference."[12]

Box 2. Ovarian Cancer Types

Epithelial ovarian cancer
- Serous carcinoma
  - –High-grade serous carcinoma
  - –Low-grade serous carcinoma
- Endometrioid carcinoma
- Mucinous carcinoma
- Clear-cell carcinoma
- Borderline or low-malignant-potential neoplasms
- Carcinosarcoma
- Undifferentiated or dedifferentiated
- Transitional cell carcinoma (Brenner tumor)

Germ-cell tumors
- Dysgerminoma
- Immature teratoma
- Embryonal carcinoma
- Endodermal sinus or yolk sac tumors

Sex cord–stromal tumors
- Granulosa cell tumors
- Thecomas
- Sertoli-Leydig cell tumors

RISK FACTORS

Age

With some exceptions, ovarian cancer is generally a disease of older age, with more than 88% of cases diagnosed after age 45 years.[4] For children and young adults, the incidence of malignant ovarian cancer of any type is very low. Girls and young women aged 0–14 years, 15–19 years, and 20–24 years have an incidence of only 3.7, 13.7, and 17.3 cases per 1,000,000 females, respectively.[13] Overall incidence of ovarian cancer increases over a woman's lifetime, peaking in the seventh decade of life, with a median age at diagnosis of 63 years.[4,5] The age at peak incidence varies significantly by histologic type; for germ-cell ovarian cancers, it is in the second decade of life; for sex cord–stromal ovarian cancers, it is in the sixth decade; for epithelial ovarian cancers, peak incidence occurs in the seventh and eighth decades.[14]

Lifestyle

No specific diet has been consistently associated with increases or decreases in the risk of ovarian cancer. Current data do not show an increased risk of ovarian cancer with alcohol use.[15–17] Although a number of reviews and individual studies of obesity and the risk of ovarian cancer have shown an association, results have been inconsistent,[18–20] possibly because of unmeasured obesity-related confounding risk factors. Increased physical activity has been associated with decreased risk of ovarian cancer, and inactivity has been associated with increased risk. The strongest data supporting an inverse association between physical activity and the risk of ovarian cancer come from case–control studies. In a review, data from included

case–control studies demonstrated risk reductions of at least 20% among women who are regularly active.[21] Some studies report an association between smoking and increased risk of mucinous ovarian cancer and decreased risk of clear-cell carcinoma. These associations have been difficult to study given the small number of cases and the many subtypes of ovarian cancer.[22] Our review found heterogeneity in the studies on the use of talcum powder and ovarian cancer risk (Appendix 3, http://links.lww.com/AOG/D170, provides a complete evidence summary).

Hormonal

Endogenous Hormones

In a population-based, case–control study, parous women had a significant reduction of ovarian cancer risk (odds ratio [OR] 0.4, 95% CI 0.3–0.6 vs nulliparous women).[23] Later age at menarche and earlier age at menopause have been shown to significantly decrease the risk of ovarian cancer. In a case–control study, the OR was 0.8 (95% CI 0.6–1.0) for women reporting menarche at age 15 years or older compared with women reporting menarche at age 12 years or younger.[24] Women who reported menopause before age 45 years had an OR of ovarian cancer of 0.6 (95% CI 0.5–0.9) compared with women who reported menopause at age 45 years or older.[24]

Breastfeeding appears to have a protective effect for women at both average and high risk.[25,26] In women at average risk, a meta-analysis of 19 studies including a total of 469,095 women reported a 24% reduction in ovarian cancer among those who breastfed (95% CI 0.69–0.83), and a longer duration of breastfeeding was associated with decreased risk of ovarian cancer.[26] In a 2021 systematic review and meta-analysis investigating breastfeeding and the risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers, the overall pooled OR of ever having breastfed among patients who had ovarian cancer was 0.767 (95% CI 0.688–0.856) for patients with *BRCA1* mutations and 0.817 (95% CI 0.650–1.028) for patients with *BRCA2* mutations.[27] In a study of two prospective cohorts, breastfeeding for 18 months or more compared with never breastfeeding was associated with a significantly decreased risk of ovarian cancer (relative risk [RR] 0.66, 95% CI 0.46–0.96). For each month of breastfeeding, the RR decreased by 2% (RR 0.98, 95% CI 0.97–1.00).[28]

Menopausal Hormone Therapy

Postmenopausal hormone therapy (HT) has consistently been associated with an increased risk of ovarian cancer. In a meta-analysis of 42 studies that included 12,238 cases of ovarian cancer, estrogen-only HT was associated with a 1.28-fold increased risk (95% CI 1.18–1.40) of developing epithelial ovarian cancer, and estrogen–progestin HT was associated with a 1.11-fold (95% CI 1.02–1.21) increased risk.[29] Guidelines for the use of HT were beyond the scope of our evidence review. Use of HT requires a much broader assessment of risks and benefits than included here.

Combined Oral Contraceptives

Multiple studies and systematic reviews have consistently shown decreased ovarian cancer risk with hormonal contraceptive use in women at average and high risk.[30–34] In women at average risk, a 2013 meta-analysis noted a significant reduction in ovarian cancer incidence in ever-users compared with never-users of oral contraception (OR 0.73, 95% CI 0.66–0.81), with a 50% reduction noted after 10 or more years of use.[35] In an analysis of six case–control studies, the risk reduction in ovarian cancer increased with longer duration of oral contraceptive use (OR 0.83, 95% CI 0.69–1.01 for use for less than 5 years; OR 0.42, 95% CI 0.30–0.59 for use for 5 years or longer vs nonuse).[36] In women at high risk, a meta-analysis of 18 studies involving 1,503 cases of ovarian cancer found that oral contraceptive use was associated with a significantly reduced risk of ovarian cancer in women with a *BRCA1* or *BRCA2* mutation (summary RR 0.50, 95% CI 0.33–0.75), with an additional risk reduction of 36% for each additional 10 years of use (RR 0.64, 95% CI 0.53–0.78).[37] In another meta-analysis of three case–control studies, there was a significantly reduced risk of ovarian cancer in *BRCA1* and *BRCA2* mutation carriers with any past use of combined oral contraceptives (OR 0.57, 95% CI 0.47–0.70). This same study also demonstrated a reduced ovarian cancer risk with a longer duration of use (OR 0.95, 95% CI 0.93–0.97; $P<.001$).[38]

Intrauterine Devices and Progesterone-Only Contraception

A 2021 meta-analysis that included three prospective cohort studies found no difference in cancer risk between levonorgestrel intrauterine system users and never-users (OR 0.66, 95% CI 0.41–1.08).[39] A second meta-analysis of 11 studies found decreased risk with intrauterine device use (OR 0.68, 95% CI 0.62–0.75). However, this study pooled all types of intrauterine devices and combined both cohort and case–control studies.[40] In a prospective cohort study of women from Denmark, use of progesterone-only contraceptives was not associated with ovarian cancer risk

(276,221 person-years, adjusted RR 0.87, 95% CI 0.59–1.29).[41]

Tubal Ligation

Tubal ligation is associated with decreased risk of ovarian cancer. In a meta-analysis of 13 studies, having a tubal ligation was associated with a 34% decreased risk of epithelial ovarian cancer (RR 0.66, 95% CI 0.60–0.73).[42]

Family History and Genetic Mutations

The risk of ovarian cancer is increased with certain genetic mutations. About 10–25% of ovarian cancers are associated with a hereditary genetic abnormality.[9] Although multiple germline mutations are associated with ovarian cancer, *BRCA1* and *BRCA2* germline mutations are the most common and are found in 10–15% of women with ovarian cancer.[9,43,44] A woman with a *BRCA1* mutation has a 39–58% lifetime risk of ovarian cancer, whereas a woman with a *BRCA2* mutation has about a 13–29% lifetime risk.[45] *BRIP1*, *RAD51C*, and *RAD51D* have also been associated with an increased risk of ovarian cancer. Mutations in these three genes are estimated to be associated with 2% of ovarian cancer cases.[46] Other genetic mutations and the absolute risk of epithelial ovarian cancer are shown in Table 1.[45]

Table 1. Ovarian Cancer Risk by Genetic Mutation

Gene	Epithelial Ovarian Cancer Absolute Risk*
ATM	<3%
BRCA1	39%–58%
BRCA2	13%–29%
BRIP1	>10%
MLH1, MSH2	>10%
MSH6	≤13%
PMS2	<3%
EPCAM	<10%
PALB2	3%–5%
RAD51C	>10%
RAD51D	>10%

* Modified with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for genetic/familial high-risk assessment: breast, ovarian and pancreatic v2.2022. © 2022 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Family history of ovarian cancer without an identified inherited genetic mutation is also associated with increased ovarian cancer risk. In a case–control study that included 554 patients, ovarian cancer in a first-degree relative (mother or sister) was associated with a 2.4-fold increased risk (95% CI 1.4–4.1).[47,48]

Health History

Infertility

A 2020 meta-analysis including nine prospective cohort studies and 10,383 patients with ovarian cancer found that the RR of ovarian cancer was 1.51 (95% CI 1.35–1.69) in patients with infertility with low heterogeneity.[49] It is not clear whether infertility is an independent risk factor or whether the observed effect is mediated by nulliparity, endometriosis, decreased contraceptive use, and other risk factors. The American Society for Reproductive Medicine guideline states that, according to available data, there is no significant increased risk of ovarian cancer after the use of fertility drugs, but there potentially may be a small increased risk of borderline ovarian tumors.[50] In a large cohort study evaluating the incidence of borderline ovarian tumors in patients undergoing in vitro fertilization (IVF) identified through a hospital registry, the rate of borderline ovarian tumors in women undergoing IVF compared with patients not undergoing IVF was higher with a hazard ratio of 2.46 (95% CI 1.20–5.04).[51] Similarly, in another cohort of more than 19,000 women undergoing IVF, compared with the general population, the incidence of borderline tumors was higher (standardized incidence ratio 1.76, 95% CI 1.16–2.56).[52]

Endometriosis

Consistent data suggest an association between endometriosis and invasive ovarian carcinoma. In a meta-analysis including 40,609 cases of ovarian cancer, Wang et al[53] found an association between endometriosis and epithelial ovarian cancer (OR 1.42, 95% CI 1.28–1.57). There appears to be a stronger association of endometriosis with clear-cell carcinoma.[53–56]

Other Medications

Aspirin use has been associated with a slightly lower risk of ovarian cancer in observational studies[57,58] (Appendices 3 and 4, http://links.lww.com/AOG/D170, provide complete evidence summaries involving risk factors). In a large cohort study using Korean National Health Insurance Service data, β-blocker use has also been associated with better survival outcomes in ovarian cancer in cases of long-term duration of use and in older patients.[59]

RISK REDUCTION

A 2009 meta-analysis showed an 80% reduction in the incidence of ovarian cancer after risk-reducing bilateral salpingo-oophorectomy (BSO) in *BRCA1* and *BRCA2* carriers (95% CI 0.12–0.39).[60] Risk-reducing BSO is recommended by ACOG, the National Comprehensive Cancer Network, and the Society of Gynecologic Oncology for women at increased risk of ovarian cancer (Box 3).[45,61,62] Several studies have explored the safety of the procedure and concerns about the effects of estrogen deprivation and quality of life.[63–65] Other than an increase in hot flushes and vaginal dryness, there were no reported significant risks to the procedure.

Although the feasibility of complete salpingectomy compared with standard postpartum tubal ligation at cesarean delivery has been demonstrated,[66] our review did not find any prospective studies of ovarian cancer risk reduction with opportunistic salpingectomy alone among either women at high risk or

Box 3. Recommendations for Ovarian Cancer Risk Reduction

National Comprehensive Cancer Network*

Risk-reducing BSO:

- "*BRCA* pathogenic/likely pathogenic variant-positive management: Recommend risk-reducing salpingo-oophorectomy, typically between 35 and 40 years, and upon completion of childbearing. Because ovarian cancer onset in patients with *BRCA2* pathogenic/likely pathogenic variants is an average of 8–10 years later than in patients with *BRCA1* pathogenic/likely pathogenic variants, it is reasonable to delay RRSO for management of ovarian cancer risk until age 40–45 years in patients with *BRCA2* pathogenic/likely pathogenic variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery." (page BRCA-A 2 of 3)
- Consider between the ages of 45 and 50 years in carriers of a *BRIP1* variant (12% lifetime risk), an *RAD51C* variant (11% lifetime risk), and an *RAD51D* variant (13% lifetime risk).
- Total hysterectomy or BSO may be considered in those who have completed childbearing and carry a mismatch repair gene linked to Lynch syndrome.

SDO: Salpingectomy alone is not recommended for risk reduction.

Society of Gynecologic Oncology†

Risk-reducing BSO: Recommend risk-reducing BSO "be performed between 35 and 40 years of age in women with *BRCA1* and *BRCA2* mutations. Guidance for women who are at high risk according to strong family histories or who have been identified with a genetic mutation other than *BRCA1* or *BRCA2* generally follows the guidelines for *BRCA1* and *BRCA2* mutation carriers, but there are fewer data for these groups to support the value of salpingo-oophorectomy. Some syndromes such as Peutz-Jeghers syndrome are associated with cancer at a younger age, so the timing of RRSO should be individualized according to the age of incident cancers in the family or the specific mutation. Flexibility in the timing of RRSO may also be appropriate for *BRCA2* carriers who present with ovarian cancer at a later age than BRCA1 carriers." (page 2112)

SDO: "Can be considered at the completion of childbearing in women at increased genetic risk of ovarian cancer who do not agree to salpingo-oophorectomy. However, this is not a substitute for oophorectomy, which should still be performed as soon as the woman is willing to accept menopause, preferably by the age of 40 years." (page 2116)

OS: "Can be considered in average-risk women undergoing hysterectomy, other pelvic surgery, or sterilization at the completion of childbearing." (page 2116)

OC use: "Women with *BRCA1* or *BRCA2* mutations should consider taking oral contraceptive pills to reduce their ovarian cancer risk." (page 2112)

American College of Obstetricians and Gynecologists‡

Risk-reducing BSO: recommend at age 35–40 years for *BRCA1* mutation carriers; women with *BRCA2* mutations may consider delaying until age 40–45 years.

OS: Salpingectomy at the time of hysterectomy or as a means of tubal sterilization appears to be safe and does not increase the risk of complications. OS should not alter the intended route of hysterectomy.

OC use: Appropriate for women with mutations in *BRCA1* or *BRCA2* if indicated. Use for cancer prophylaxis is reasonable.

BSO, bilateral salpingo-oophorectomy; RRSO, risk-reducing salpingo-oophorectomy; SDO, salpingectomy with delayed oophorectomy; OS, opportunistic salpingectomy; OC, oral contraceptive.

*National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 2.2021. Accessed May 15, 2022. https://nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

†Walker JL, Powell CB, Chen LM, Carter J, Bae Jump VL, Parker LP, et al. Society of Gynecologic Oncology recommendations for the prevention of ovarian cancer. Cancer 2015;121:2108–20. doi: 10.1002/cncr.29321

‡Hereditary breast and ovarian cancer syndrome. Practice Bulletin No. 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110–26. doi: 10.1097/AOG.0000000000002296

those at average population risk. Existing retrospective data support that bilateral salpingectomy is at least comparable, if not superior, to bilateral tubal ligation for reducing ovarian cancer risk.[42,67] A meta-analysis from 2016 reported a significantly reduced risk of ovarian cancer in women who underwent bilateral salpingectomy compared with those who did not (OR 0.51, 95% CI 0.35–0.75).[68]

Our review did not identify data to support salpingectomy alone in women at high risk. Anecdotal evidence of an increase in the number of women at high risk being offered salpingectomy with delayed oophorectomy indicates that there is a potential false perception of decreased risk in these patients after salpingectomy, which may ultimately decrease the odds of their timely return for ovary removal.[69,70] Multiple studies are underway to evaluate the risks and benefits of salpingectomy with delayed oophorectomy in women at high risk for ovarian cancer.[71,72]

Epidemiologic evidence for potentially modifiable risk factors is summarized in the Risk Factor section. Our search found no interventional studies addressing these risk factors and no specific guidance from major professional societies. Given the well-accepted health benefits of contraception, physical activity, and lactation, it is reasonable to counsel patients on the potential secondary benefits of these activities on ovarian cancer risk (Appendix 4, http://links.lww.com/AOG/D170, provides a complete evidence summary).

SCREENING

Screening Methods That Have Been Proposed

The most common methods studied for ovarian cancer screening are transvaginal ultrasonography, bimanual palpation, and measurement of the serum tumor marker CA 125. Algorithms using a combination of transvaginal ultrasonography and tumor markers have also been studied. These algorithms include the ROCA (Risk of Ovarian Cancer Algorithm)[73] and the parametric empirical Bayes model. ROCA estimates the risk of ovarian cancer on the basis of age and change in CA 125. The algorithm makes recommendations for repeat assessment of CA 125 or transvaginal ultrasonography on the basis of the calculated risk. ROCA was initially studied in a randomized controlled trial of 13,582 women aged 50 years and older; ROCA had a specificity for epithelial ovarian cancer of 99.8% (95% CI 99.7–99.9%) and a positive predictive value of 19% (95% CI 4.1–45.6%).[73] ROCA was further studied in the prospective United Kingdom Familial Ovarian Cancer Screening Study and in a large-scale, randomized controlled trial in the United Kingdom.[74,75] The parametric empirical Bayes model also interprets serial CA 125 levels and has performed similarly to ROCA in an examination of U.K. data sets.[76]

Screening in Asymptomatic Women at Average Risk

In our review, no major professional society has recommended the use of ovarian cancer screening in asymptomatic women at average risk, nor did any individual study show clear overall benefit. Several large randomized controlled trials have examined ovarian cancer screening in patient populations at average risk. These studies include the Shizuoka Cohort Study of Ovarian Cancer Screening in Japan; the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer) screening trial in the United States; the UKCTOCS (UK Collaborative Trial of Ovarian Cancer Screening); and the U.K. pilot study that preceded the UKCTOCS. These trials have been included in several systematic reviews and meta-analyses. A 2018 systematic review was conducted by the U.S. Preventive Services Task Force for its updated publication on screening for ovarian cancer and included results from the UKCTOCS, the smaller U.K. pilot trial, and the PLCO trial. This systematic review did not include information from the Shizuoka Cohort Study in Japan because of the lack of mortality data and the significantly lower prevalence of ovarian cancer (0.31/1,000) than expected in the U.S. population.[77] The systematic review found that screening offered no benefit in terms of ovarian cancer mortality. It found that the screened group in the PLCO trial had an RR of mortality of 1.18 (95% CI 0.82–1.71) compared with the control groups, whereas the UKCTOCS trial had hazard ratios of 0.91 (95% CI 0.76–1.09) for the ultrasonography-screened group and 0.89 (95% CI 0.74–1.08) for the CA 125-screened group. A meta-analysis by Marchetti et al[78] in 2018 evaluated data on postmenopausal, asymptomatic women using data from the PLCO trial, the Shizuoka Cohort Study, and the UKCTOCS. Although the meta-analysis showed earlier stage of diagnosis with ovarian cancer screening compared with unscreened individuals in a control group (RR 1.30, 95% CI 1.14–1.49), it did not show a benefit of screening for disease-specific mortality (RR 0.96, 95% CI 0.85–1.10).[78] The meta-analysis found an increase in ovarian cancer diagnoses when the multimodal approach of CA 125 assessment with follow-up ultrasonography was performed (RR 1.39, 95% CI 1.21–1.60).[78]

Our review did not find any high-quality evidence supporting the use of other serum markers,

circulating tumor cells, or algorithms in ovarian cancer screening. The U.S. Preventive Services Task Force recommends against screening for ovarian cancer in asymptomatic women who are not known to have a high-risk hereditary cancer syndrome, concluding that "there is at least moderate certainty that the harms of screening for ovarian cancer outweigh the benefits."[79]

Screening in Patients at High Risk

We found no randomized controlled trials of ovarian cancer screening in women at high risk. Secondary analysis of the PLCO cancer screening trial data revealed similar rates of abnormal ovarian cancer screening with ultrasonography and CA 125 evaluation across all risk groups and no difference in overall or disease-specific mortality.[80,81] The University of Kentucky Ovarian Cancer Screening Trial, which used screening ultrasonography and CA 125 assessment, reported increased 5- and 10-year survival rates for patients with screening-detected epithelial ovarian cancer compared with unscreened patients with epithelial ovarian cancer; however, this study was not randomized, lacked a control group, and did not describe patients' cancer histology.[82,83]

Because of the lack of efficacy of ovarian cancer screening in patients at high risk, none of the professional societies included in this review explicitly recommend ovarian cancer screening for this population; however, several state that ovarian cancer screening can be offered to patients at high risk (Table 2).

Several organizations support identifying women at high risk. The ACOG, the National Comprehensive Cancer Network, the National Institute for Health and Care Excellence, and the Society of Obstetricians and Gynaecologists of Canada recommend genetic counseling on the basis of family history of breast or ovarian cancer or both (Table 2).[45,61,84–90] High-risk women can be identified by cancer risk assessments that include all cancers in the family history. Genetic testing can then discover pathogenic mutations in genes that increase the risk of epithelial ovarian cancer. Currently, the National Comprehensive Cancer Network lists *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *DICER1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *RAD51C*, and *RAD51D* as genes associated with moderate or high risk for ovarian cancer[45] (Appendix 5, http://links.lww.com/AOG/D170, provides a complete evidence summary).

EARLY DIAGNOSIS

In a systematic review of published studies of symptoms associated with ovarian cancer, the presence of an abdominal mass (positive likelihood ratio [LR] 30.0), abdominal distention or increased girth (positive LR 16.0), and abdominal or pelvic pain (positive LR 10.4) had the highest LRs associated with an ovarian cancer diagnosis. The specificities associated with these symptoms range from 88% to 99%; however, the sensitivities were all less than 50%.[91] Indices have been developed that combine symptoms and their duration to improve prediction. The Goff Ovarian Cancer Symptom Index (combined sensitivity 63%, specificity 95%, positive LR 12.6) and the Grewal symptom score (combined sensitivity 73%, specificity 91%, positive LR 8.37) have been independently validated.[91] According to a secondary analysis of UKCTOCS data, survival appears to be worse in patients who report more than one symptom at the time of diagnosis and in those who met criteria for a symptom index.[92]

Professional society guidelines about when to initiate an evaluation on the basis of symptoms vary. The ACOG states that patients and clinicians "should maintain an appropriate level of suspicion when … signs and symptoms of ovarian cancer are present."[93] Ultrasonography of the pelvis (transabdominal and transvaginal with duplex Doppler) is the most frequently recommended imaging modality for the evaluation of patients with symptoms.[10,11,94–98] The U.K. National Institute for Health and Clinical Excellence guidelines differ in that they recommend that clinicians "measure serum CA 125…in women with symptoms that suggest ovarian cancer. If serum CA 125 is 35 international units/mL or greater, arrange an ultrasound scan of the abdomen and pelvis."[96] We found no high-quality studies comparing imaging, biomarkers, risk algorithms, or multimodal risk assessment tools for the primary evaluation of patients with symptoms associated with ovarian cancer.

Appendix 6, http://links.lww.com/AOG/D170, summarizes studies and society guidelines for patients with an incidental finding of an ovarian cyst on imaging using various methods, including transvaginal ultrasonography, biomarkers, biomarker assays, and multimodal risk assessment, to exclude ovarian cancer. The studies had a number of limitations, including being conducted in patients who underwent surgery, limiting understanding of how the strategies perform in expectantly managed patients.[99] The study populations also frequently had a higher ovarian cancer incidence than expected, which may overestimate diagnostic accuracy.[99] CA 125 is the most frequently measured serum marker for the evaluation and early diagnosis of ovarian cancer despite variation in its measured sensitivity (61–90%) and specificity (71–

Table 2. Identification and Screening of High-Risk Patients

Source	Recommendations
ACOG*	Recommends genetic counseling based on family and personal histories Routine ovarian cancer screening is not recommended, but transvaginal ultrasonography or CA 125 level assessment can be considered starting at age 30–35 y until RRSO. No consensus on ovarian cancer screening in patients with Lynch syndrome
ACR 2017 Appropriateness criteria†	No effective ovarian cancer screening Ovarian cancer screening with pelvic ultrasonography may be appropriate for some premenopausal or postmenopausal women at increased risk for ovarian cancer, which includes those with a personal history or family history of ovarian cancer, known or suspected genetic predisposition, or elevated CA 125 level.
ASRM/SGO‡	No strong evidence for effective ovarian cancer screening Transvaginal ultrasonography and CA 125 level assessment may be an option for women who decline or defer RRSO.
ESMO§	No strong evidence for effective ovarian cancer screening Transvaginal ultrasonography and CA 125 every 6 mo can be considered from age 30 with proper counseling on the lack of efficacy.
NCCN‖	Recommends genetic counseling based on family and personal histories No strong evidence for effective ovarian cancer screening If RRSO is not chosen, transvaginal ultrasonography and CA 125 assessment for ovarian cancer screening may be considered starting at age 30–35.
NICE¶	Recommends a risk assessment for patients with a family history of ovarian cancer or breast cancer in first- or second-degree relatives
RCOG#	Ovarian cancer screening should not be offered as an alternative to RRSO.
SOGC**	Recommends genetic counseling No strong evidence for effective ovarian cancer screening

ACOG, American College of Obstetricians and Gynecologists; RRSO, risk-reducing salpingo-oophorectomy; ACR, American College of Radiology; ASRM, American Society for Reproductive Medicine; SGO, Society of Gynecologic Oncology; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence; RCOG, Royal College of Obstetricians and Gynaecologists; SOGC, Society of Obstetricians and Gynaecologists of Canada.

* Hereditary breast and ovarian cancer syndrome. Practice Bulletin No 182. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e110–26. doi:10.1097/AOG.0000000000002296; *and* Lynch syndrome. Practice Bulletin No. 147. American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology. Obstet Gynecol 2014;124:1042–54. doi:10.1097/01.AOG.0000456325.50739.72

† Expert Panel on Women's Imaging; Pandharipande PV, Lowry KP, Reinhold C, Atri M, Benson CB, et al. ACR Appropriateness Criteria® Ovarian Cancer Screening. J Am Coll Radiol 2017;14:S490–9. doi: 10.1016/j.jacr.2017.08.049

‡ Chen L, Blank SV, Burton E, Glass K, Penick E, Woodard T. Reproductive and hormonal considerations in women at increased risk for hereditary gynecologic cancers: Society of Gynecologic Oncology and American Society for Reproductive Medicine evidence-based review. Fertil Steril 2019;112:1034–42. doi:10.1016/j.fertnstert.2019.07.1349

§ Paluch-Shimon S, Cardoso F, Sessa C, Balmana J, Cardoso MJ, Gilbert F, et al. Prevention and screening in BRCA mutation carriers and other breast/ovarian hereditary cancer syndromes: ESMO Clinical Practice Guidelines for cancer prevention and screening. Ann Oncol 2016;27(suppl 5):v103–10.

‖ National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic version 2.2021. Accessed May 15, 2022. https://nccn.org/login?ReturnURL=https://nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

¶ National Institute for Health and Care Excellence. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. Clinical Guideline 164. 2013, updated 2019. Accessed April 8, 2022. https://www.nice.org.uk/guidance/cg164

Management of women with a genetic predisposition to gynaecological cancers. Scientific Impact Paper No. 48. Royal College of Obstetricians and Gynaecologists. Obstet Gynaecol 2015;17:140. doi: 10.1111/tog.12182

** Jacobson M, Bernardini M, Sobel ML, Kim RH, McCuaig J, Allen L. Gynaecologic management of heeditary breast and ovarian cancer. Committee Opinion No. 366. Society of Obstetricians and Gynaecologists of Canada. J Obstet Gynaecol Can 2018;40:1497–510. doi: 10.1016/j.jogc.2018.05.046

93%).[94] Sensitivity and specificity are poorer in premenopausal patients than postmenopausal patients, likely because benign conditions that can cause CA 125 elevation occur more frequently in premenopausal patients than postmenopausal patients and the ovarian cancer incidence is lower in premenopausal patients than in postmenopausal patients.[94]

The International Ovarian Tumour Analysis Phase 5 study was a prospective, multicenter cohort study with patients selected for surgery or conservative management on the basis of morphology and symptoms.[100] In this study, 1,919 patients with a new diagnosis of a mass that was assessed as benign on ultrasonography had outcomes examined at 24 months after

enrollment. Of these, 20.2% had spontaneous resolution of their mass during follow-up, and 16.1% had surgical intervention. The risk of a missed diagnosis at surgery was less than 0.5% when defined as a final diagnosis of invasive malignancy, borderline tumor, torsion, or cyst rupture. We found no prospective studies to guide the frequency or duration of ultrasound surveillance.

We found several relevant guidelines for the management of incidentally identified masses. According to the ACOG, "transvaginal ultrasonography is the recommended imaging modality for a suspected or and incidentally identified pelvic mass. No alternative imaging modality has demonstrated sufficient superiority to transvaginal sonography to justify routine use."[94] The American College of Radiology's Ovarian-Adnexal Reporting and Data System ultrasound risk-stratification and management system recommends ultrasound follow-up, referral to an ultrasound specialist, pursuing magnetic resonance imaging, or referral to a gynecologist or gynecologic oncologist on the basis of the risk of malignancy[101] (Table 2 in Appendix 6, http://links.lww.com/AOG/D170, gives more information).

Most relevant guidelines, including the National Institute for Health and Care Excellence, the European Society for Medical Oncology, the Royal College of Obstetricians and Gynaecologists, and the Society of Obstetricians and Gynaecologists of Canada, make no mention of use of serum biomarker panels.[10,96–98] The ACOG states, "Serum biomarker panels may be used as an alternative to CA 125 level alone in determining the need for referral to or consultation with a gynecologic oncologist when an adnexal mass requires surgery. These biomarker panels are not recommended for use in the initial evaluation of an adnexal mass, but may be helpful in assessing which women would benefit from referral to a gynecologic oncologist"[94] (Appendix 6, http://links.lww.com/AOG/D170, gives a complete evidence summary).

HEALTH DISPARITIES

Significant ovarian cancer health disparities were noted in the evidence review across the continuum of care and are often linked to nonadherence to guidelines from the National Comprehensive Cancer Network. Black patients, those with low socioeconomic status, and those who do not have private insurance are among the populations who often receive less treatment.

Black women consistently had worse outcomes and less improvement in survival over time compared with their White counterparts. We found little evidence regarding other racial and ethnic groups (eg, Hispanic White women and Asian and Pacific Islander women) and other socially marginalized populations. Our review found no articles meeting inclusion criteria on ovarian cancer risk among individuals who do not identify as cisgender or female. These findings were important enough that panel members and stakeholder representatives agreed that the topic merits its own summary. Please see the companion summary, "Health Disparities in Ovarian Cancer: Report from the Ovarian Cancer Evidence Review Conference."[12]

DIAGNOSIS AND CARE COORDINATION

Features that help stratify risk of malignancy and guide management include patient characteristics, physical examination findings, imaging results, and serum tumor marker levels.[94] Patient history should include a thorough personal medical and gynecologic history, family history, and review of symptoms.[94] A thorough physical examination should include palpation of cervical, supraclavicular, axillary, and groin lymph nodes; a pulmonary examination; palpation and auscultation of the abdomen; and a pelvic examination with visual inspection of the perineum, cervix, and vagina, as well as a bimanual examination that includes a rectovaginal examination if indicated. Masses that are irregular, firm, fixed, nodular, bilateral, or associated with ascites are more concerning for malignancy.[94]

Transvaginal ultrasonography is typically the most appropriate initial imaging modality for the assessment of adnexal masses. Features that are concerning for malignancy include papillary or solid components, irregularity, presence of ascites, and high color Doppler flow. Magnetic resonance imaging may further distinguish benign from malignant masses, especially if they are indeterminate on ultrasonography, and may help establish the origin if it is not clearly adnexal.[102] Computed tomography is useful to assess for the extent of metastatic disease, to evaluate for a potential other primary site, and to plan for surgery.[94] Baseline blood tests should include a complete blood count, chemistry profile with liver function tests, and tumor marker assessment.

Accurately predicting malignancy in asymptomatic and symptomatic masses is difficult. The National Comprehensive Cancer Network recommends that "because the primary assessment and debulking by a gynecologic oncologist is associated with improved survival, all patients with lesions suspected to be ovarian malignancies (based on clinical evidence) should

be referred to an experienced gynecologic oncologist for evaluation."[5] The ACOG recommends either consultation with or referral to a gynecologic oncologist for those with an adnexal mass who meet one or more of the following criteria:[94]Any patient with ultrasound findings suggestive of malignancy, ascites, a nodular or fixed pelvic mass, or evidence of abdominal or distant metastasisPostmenopausal patient with elevated CA 125 levelPremenopausal patient with a very elevated CA 125 levelAny patient with an elevated score on a formal risk assessment test such as the multivariate index assay, Risk of Malignancy Index, or the Risk of Ovarian Malignancy Algorithm or one of the ultrasound-based scoring systems from the International Ovarian Tumor Analysis Group

Multiple studies have demonstrated that having a gynecologic oncologist involved in the care of patients with ovarian cancer increases survival and offers other advantages. Surgery by a gynecologic oncologist has consistently been associated with higher rate of optimal tumor debulking, improved long-term and overall survival, higher likelihood of undergoing a staging surgery if appropriate, higher likelihood of receiving chemotherapy, and increased likelihood of receiving guideline-concordant care.[103–108]

After referral to a gynecologic oncologist, the trajectory of management typically depends on whether the disease is isolated or metastatic and the individual patient's fertility wishes, functional status, medical comorbidities, and goals. Management decisions for patients with ovarian cancer involve important, complex, and subtle nuances that must be carefully considered.

For patients with apparent early-stage disease, comprehensive surgical staging typically includes a thorough abdominal exploration, aspirating ascites or obtaining pelvic washings, peritoneal biopsies, and omentectomy, with pelvic and para-aortic lymphadenectomy for most histologies except mucinous carcinoma, granulosa cell tumors, and borderline tumors.[5]

For patients with advanced disease, primary tumor debulking surgery and neoadjuvant chemotherapy may be options. This decision is a complex, nuanced one (Appendix 6, http://links.lww.com/AOG/D170). For patients who are good surgical candidates and have metastatic disease that is surgically resectable, surgical debulking is typically recommended. For patients who are poor surgical candidates or in whom the likelihood of a complete surgical cytoreduction is low, neoadjuvant chemotherapy may be appropriate.[5,109] Evaluation by a gynecologic oncologist is recommended to inform this decision before initiation of neoadjuvant chemotherapy. Laparoscopy can also be a useful tool to evaluate the feasibility of optimal cytoreduction.

Consideration of clinical trials whenever possible is recommended for all patients with ovarian cancer.[5] In general, adjuvant chemotherapy is recommended for most patients with ovarian cancer except patients with low-grade stage IA or IB ovarian cancer and those with select histologies.[5] Adjuvant chemotherapy for epithelial cancer typically consists of intravenous carboplatin and paclitaxel. Determining the optimal number of cycles, dosing, and frequency of chemotherapy is complex, so counseling by a gynecologic oncologist is important.[5] Incorporation of bevacizumab and poly (ADP-ribose) polymerase inhibitor maintenance may be considered in advanced disease.[5]

Patients with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer should also have genetic risk evaluation and germline and somatic testing.[5] Because most patients with ovarian cancer will undergo surgery and chemotherapy at some point, the primary care practitioner can play an important role in optimizing the status of the patient to undergo such treatment[5] (Appendix 7, http://links.lww.com/AOG/D170, provides a complete evidence summary).

SPECIAL CONSIDERATIONS

In women in whom early-stage ovarian cancer presents before completion of childbearing, it is appropriate to consider avoiding the traditional radical surgical approach of a hysterectomy, BSO, and comprehensive surgical staging in favor of fertility-sparing surgery, which typically consists of a unilateral salpingo-oophorectomy with surgical staging and allows retention of the unaffected ovary and uterus.[110] When this approach is reserved for patients with early-stage disease, recurrence rates and survival are similar to those found in patients treated with conventional surgery.[110,111] Obstetric outcomes after fertility-sparing surgery typically mirror the baseline population rate.[112] The National Comprehensive Cancer Network recommends considering fertility-sparing surgery for patients who wish to preserve fertility and have apparent early-stage disease or low-risk tumors such as early-stage invasive epithelial tumors, low-malignant-potential lesions, malignant germ-cell tumors, or malignant sex cord–stromal tumors.[5] The American Society of Clinical Oncology also provides guidelines for using fertility-sparing surgery on the basis of histology and stage.[95]

After treatment for ovarian cancer, patients contend with varied residual symptoms, including increased rates of depression and anxiety.[113] Physical symptoms after completion of treatment can include

residual neuropathy, pelvic pain, fatigue, nausea, and decreased libido.[114,115] Sexuality is dramatically affected by surgical treatment for ovarian cancer. In one systematic review, 47% of patients reported little or no sexual desire, 62% reported pain with sex, and 80% reported vaginal dryness.[116] General well-being can also suffer because ovarian cancer may affect patients' employment and financial health.[115] The Society of Gynecologic Oncology describes methods for assessing social needs affecting quality of life among patients with gynecologic malignancies, including financial, psychological, and spiritual needs; issues with job, transportation, food, housing, and utility insecurities; and caregiver burden.[117]

Premenopausal patients who undergo BSO during their course of treatment will usually experience an abrupt surgical menopause, and the associated vasomotor symptoms can contribute to physical discomfort.[118] In a statement endorsed by the North American Menopause Society, the Society of Gynecologic Oncology states that estrogen therapy can be prescribed for most women with epithelial ovarian cancer. Hormone therapy is not recommended for patients with low-grade serous and endometrioid ovarian cancers because those cancers may respond to treatment with antiestrogen therapies. The Society of Gynecologic Oncology states that there are insufficient data to make a recommendation for HT in women with a history of borderline tumors of the ovary.[119] For patients at high risk who elect risk-reducing salpingo-oophorectomy before menopause and who do not have a personal history of hormone-sensitive breast cancer precluding HT use, the decision to use HT should be individualized and account for the effects of early menopause on long-term health and wellness, in addition to any increased risk for breast cancer.[112]

For women who are awaiting treatment or for those who undergo fertility-sparing surgery, the Centers for Disease Control and Prevention's Medical Eligibility Criteria for Contraceptive Use considers all contraceptives to be category 1 in the setting of ovarian cancer, meaning that there is no restriction for the use of the contraceptive method[120] (Appendix 8, http://links.lww.com/AOG/D170, provides a complete evidence summary.)

RESEARCH GAPS AND OPPORTUNITIES

The evidence review and stakeholder discussion identified many research gaps and opportunities for ovarian cancer, the highest priority of which are listed here (Appendices 2–8, http://links.lww.com/AOG/D170, provide a more thorough analysis of research gaps and opportunities for each topic).Understand the epidemiology of and risk factors for ovarian cancer in the transgender communityConduct intervention trials of preventive measures in women at high or average riskObtain prospective data on opportunistic salpingectomy at the time of bilateral tubal sterilization or other pelvic surgeryCollect data on salpingectomy with delayed oophorectomy in patients with *BRCA1* and *BRCA2* mutationsDevelop effective screening or early diagnosis strategies for patients at average and high riskRefine risk stratification in patients at high riskOptimize methods to evaluate and manage adnexal masses that are found incidentallyOptimize ovarian cancer screening for individuals at high risk who choose to delay or forego risk-reducing salpingo-oophorectomyRefine and standardize criteria for patient referralEducate health care practitioners about which patients would benefit from subspecialty referralDevelop best practices to mitigate ovarian cancer treatment-related changes in sexualityImprove the understanding of stigma after hysterectomy for ovarian cancer and develop best practices to enhance body-positive treatment

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PEER REVIEW HISTORY

Received August 31, 2022. Received in revised form November 29, 2022. Accepted January 19, 2023. Peer reviews and author correspondence are available at http://links.lww.com/AOG/D171.